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# E. MERCK'S ANNUAL REPORT

:: OF RECENT ADVANCES IN ::  
PHARMACEUTICAL CHEMISTRY  
:: :: AND THERAPEUTICS :: ::

Biological  
& Medical  
Section

VOLUME XXV

1887



1911

E. MERCK, CHEMICAL WORKS, DARMSTADT 1912







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# Prefatory Note

to

## E. Merck's Annual Report

Volume XXV.

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As far back as 1870 I undertook to furnish my friends and customers with short reports on recent therapeutic preparations, as at that time the professional journals did not contain as detailed and complete accounts of recent discoveries in the field of pharmacotherapy as is now the case. These communications, which appeared at irregular intervals, developed in the course of years into the regular Annual Report. Its aim from the first was to collect the most important items from the entire international literature, all the information that was likely to prove of interest to physicians and pharmacists, and to present it in a perfectly, impartial manner, leaving the reader to examine the information and to decide upon its actual value. I have therefore scrupulously avoided expressing my own views upon the results obtained by others, provided these communications did not conceal some actual danger, to which it was absolutely necessary to draw attention. On account of this impartiality, combined with as comprehensive a report as possible, the Annual Report has been so highly appreciated that the number of copies printed has had to be increased from year to year. At the present time it is published in four languages (German, English, French and Russian), the total annual edition amounting to 60,000 copies.

This steady increase of the annual edition is evidence that the Annual Report supplies a real want. Further, it bears eloquent testimony that the Annual Report has succeeded in satisfying its readers.

In accordance with the purely scientific object of the Annual Report, only those new preparations and drugs have been discussed which have been introduced into therapeutics as a result of scientific research, while secret remedies and scientifically questionable preparations have been excluded as far as possible. Thus doubtful preparations will not receive unmerited recognition, such as might result from their mention in the Annual Report, which is held in such high esteem. However, all those preparations for which, in my opinion, scientific interest may be claimed, have been discussed in the Annual Report in a most impartial manner, even those which must be considered direct rivals to my

own special preparations. Not a few readers of the Annual Reports have therefore been under the impression, and some are still of the opinion, that all the preparations described in the Annual Reports are prepared by me. Some are unable to grasp the fact that the Annual Report neither is, nor is meant to be, an advertisement, but that it only fulfils the unselfish task of acquainting my friends with everything worth knowing in the field of pharmacotherapy, and not only with the substances prepared in my factory.

It sometimes happens that a new drug is mentioned in the Annual Report and excites great interest before it has been put on the market. It is quite possible in such cases that on account of unforeseen difficulties in its manufacture, or for some other reason, the drug is not put on the market at all. I therefore wish expressly to point out that in discussing a substance not of my own preparation I do not, as many apparently imagine, bind myself to supply it. If a new drug has been discussed in the literature of the past year, it must be mentioned in the Annual Report, whether it is absolutely certain to be put on the market or not. Any other procedure would certainly often be regarded as incomplete. Therefore, whenever I know that any preparation specified in the Annual Report is not on the market, I shall make a point of mentioning it in future. But as a long time may elapse between the compilation and the publication of the Annual Report, it should be noted that a preparation designated in the Report as unobtainable may possibly be obtainable in the market at the time of appearance of the Annual Report.

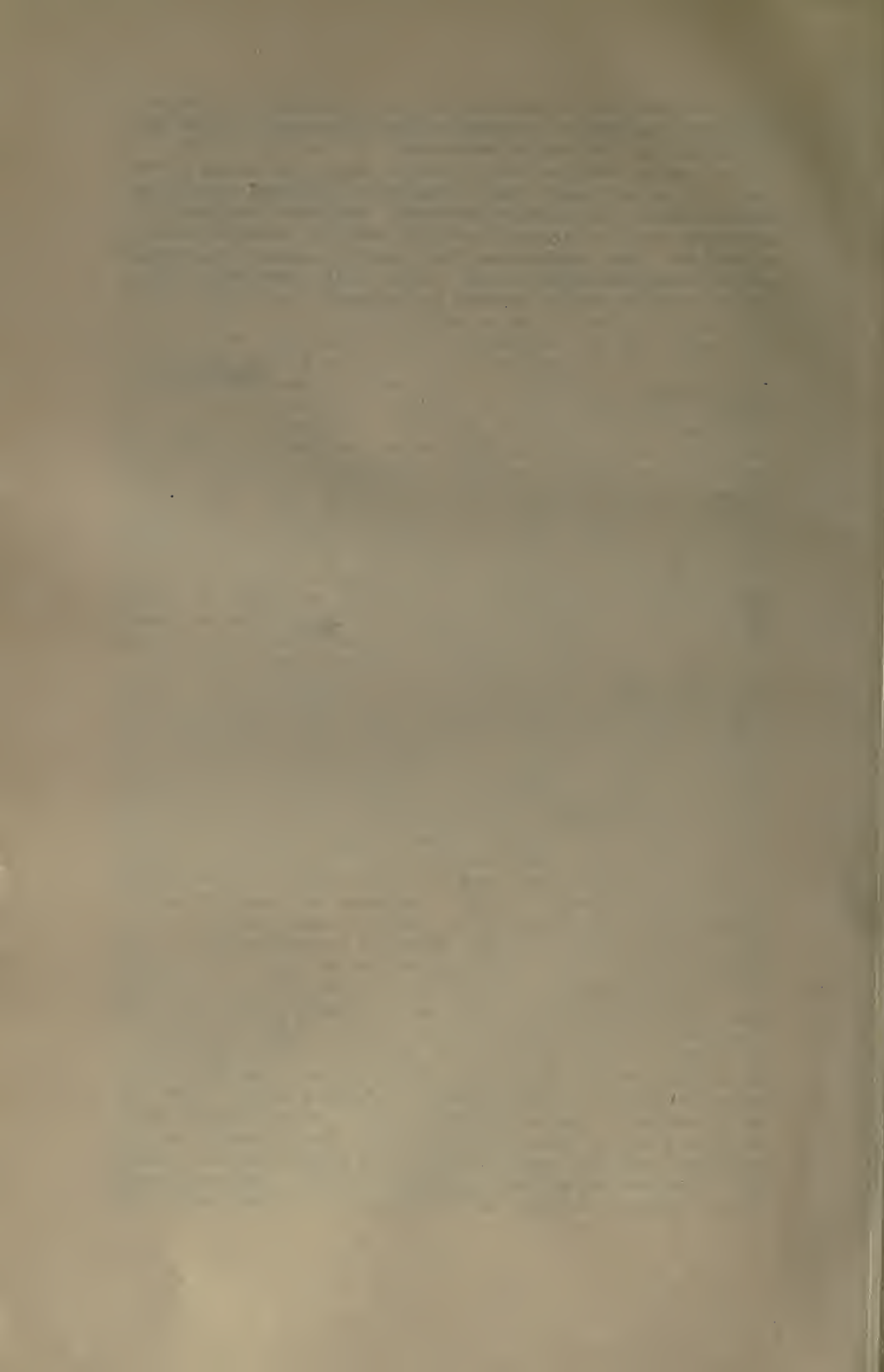
As in the course of time it became apparent that the Annual Report was incomplete, as it only took into consideration the literature of the preceding year, so that many references did not seem sufficiently clear and complete apart from the literature from which they were abstracted, I decided to increase the value of the Annual Report by the addition of special articles, in which certain groups of drugs are discussed as fully as possible, with reference to the original literature. Reference can then be made to these in future Annual Reports, thus enabling those interested to become fully acquainted with a certain field of pharmacological research and to trace the further development of the treatment in question. Thus in recent years I have presented special articles relating to organotherapy, serum therapy, and to preparations of cacodylic acid and kephir, and in this Report to the salts of glycerophosphoric acid, and to digitalis glucosides and allied drugs (the so-called digitalin group). The choice of subjects depended upon their intrinsic interest and upon the enquiries I have received in the course of the last few years.

For the benefit of those readers who have collected my Annual Reports, I would point out that the German edition of this year's Report contains a General Index of the whole series of 25 Annual Reports. This Supplement, a copy of which will be sent on request, should prove of special value to the busy practitioner, as it will enable him quickly to survey the field of modern pharmacotherapy, which is growing ever more involved. But the present Report, on account of its manifold contents, should

offer him sufficient opportunity to attain this end. I therefore confidently hope that my Annual Reports will not only retain their old friends, but will acquire new ones.

The Annual Report usually appears about the middle of the year, and is presented free of charge to scientific institutions, libraries, clinics, physicians, pharmacists, wholesale druggists, etc. (sometimes only on request). It can also be obtained through booksellers. Back numbers are only sent by special request and provided copies are still in stock. Series of the remaining editions can now only be sent to scientific institutions.

E. MERCK.



# The Glycerophosphates.

## Part I. Chemical.

Among the theoretically possible glycerides of phosphoric acid the only one which has acquired significance is the monoglyceride of phosphoric acid of the composition  $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{O} \cdot \text{PO}(\text{OH})_2$ . This compound, briefly called "glycerophosphoric acid", was discovered by Pelouze in 1846 while revising the published data relating to glycerosulphuric acid ( $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{O} \cdot \text{SO}_2 \cdot \text{OH}$ ). He found that the glycerin became hot, not only when mixed with concentrated sulphuric acid, but also when brought in contact with phosphorus pentoxide and metaphosphoric acid, from which he concluded that a glycerophosphoric acid analogous with glycerosulphuric acid must exist, and he proved the truth of this conjecture experimentally by preparing glycerophosphoric acid from glycerin and phosphoric anhydride. About the same time Goble made the interesting observation that the presence of glycerophosphoric acid could be demonstrated in yolk of egg in the form of its ammonium and calcium salts. As I shall explain more fully below, however, glycerophosphoric acid is not contained as such in yolk of egg, but combined with choline as lecithin.

When the glycerophosphates (the salts of glycerophosphoric acid) were found to be of use in therapeutics, closer attention was given to their composition. Thus J. L. W. Thudichum and C. T. Kingzett have described the preparation of calcium glycerophosphate from cephaline (a

Pelouze, *Comptes rendus de l'académie des sciences* 1846, Vol. XXI, p. 718. — *Journal für praktische Chemie* 1887, Vol. 36, p. 257.

— *Liebig's Annalen* 1846, Vol. 60, p. 321.

Goble, *Journal de pharmacie et de chimie* 1846, Vol. 9, p. 161.

— *Comptes rendus* 1846, Vol. XXI, p. 766. — *Neue Jahresberichte der Pharmazie*, Vol. 9, p. 161; Vol. 11, p. 409; Vol. 12, p. 5.

Thudichum-Kingzett, *Journal of the Chemical Society* 1876, p. 20. *Moniteur scientifique* (3), Vol. 6, p. 1274. — *Jahresbericht über Fortschritte der Chemie* 1876, p. 557.

substance contained in the brains of animals, and having the composition  $C_{42}H_{79}NPO_{18}$ ), this method is, however, very unprofitable. A. Petit and M. Polonowsky proceeded more rationally in that they used metaphosphoric acid in place of the phosphorus pentoxide suggested by Pelouze; this does not act so violently on the glycerin and obviates its partial decomposition. Besides these, Delage and Gaillard, Portes and Prunier, Carré, Willstätter, Adrian and Trillat, Astruc, Mundorf and others, have worked out methods for the preparation of glycerophosphoric acid and its salts.

While the quality and purity of the glycerophosphates were in the course of time raised to a high degree by the exertions of the manufacturers, the difficulties of their manufacture, which were by no means slight, led to frauds in the sale of the glycerophosphates, the audacity and brazenness of which have perhaps never had a parallel in the drug trade. Petit and Polonowsky, as early as 1894, worked out and published tests for the glycerophosphates, after having found that mixtures of powdered sodium phosphate and glycerin were frequently substituted for them in the market under the name of "chemically pure sodium glycerophosphate". I was also able in 1900 to expose a gross fraud which was carried on in a flourishing way by a firm in Barcelona\*). Although this firm boasted of its experience in the manufacture of glycerophosphates and mentioned specially that it was able, as opposed to its competitors, to prepare readily soluble calcium glycerophosphate, it sold as such large quantities of a mixture of 18 parts of calcium hypophosphite and 82 parts of milk sugar.

Petit-Polonowsky, *Journal de pharmacie et de chimie* 1894, II., p. 193. — *Chemiker-Zeitung* 1894, p. 1192.

Delage-Gaillard, *Nouveaux remèdes* 1896, p. 8.

Portes-Prunier, *Journal de pharmacie et de chimie* 1894, I., p. 393.

Carré, *Comptes rendus* 1903, Vol. 137, p. 1070; 1904, Vol. 138, p. 47. — *Bulletin de la société chimique* 1904, Vol. 31, p. 805.

Willstätter, *Berichte der deutschen chemischen Gesellschaft Berlin* 1904, p. 3753.

Adrian und Trillat, *Bulletin de la Soc. chim.* (3) Vol. 19, p. 684.

Astruc, *Comptes rendus de l'académie des sciences* 1905, Vol. 140, p. 727.

Mundorff, *Schweizer Wochenschrift für Pharmazie* 1896, p. 169.

Petit-Polonowsky, *Chemiker-Zeitung* 1894, p. 1192.

\*) Merck's Report 1900, p. 109.

This fraud was discovered in my laboratory and the perpetrator unmasked. These facts furnished the proof that accurate and reliable tests were absolutely necessary in order to protect the purchaser and consumer of glycerophosphates from fraud, especially as the inorganic phosphates have been proved to lack the action of the glycerophosphates partially or entirely and cannot therefore in any case be used to replace them. A reliable test for the more important of the glycerophosphates is briefly described below, which will enable every analytical chemist to confirm the excellence and purity of the glycerophosphates supplied by me.

In order to prove in an individual case whether a glycerophosphate or an inorganic phosphorus compound is present, one can proceed as follows:

A) when a soluble salt is present,

B) when an insoluble or only partially soluble preparation is present, or the salt of an organic base.

A. 2 grammes of the salt are dissolved in 100 c. c. of water at the ordinary temperature and the solution is neutralized with acetic acid or caustic soda, if it does not give a neutral reaction with litmus paper. 20 c. c. of a solution of lead acetate (10 p. c.) are then added and the mixture is well stirred. If 10 c. c. of the suspension of lead glycerophosphate thus produced be added to 2 c. c. of glacial acetic acid the precipitate is only slowly and incompletely dissolved, but if 2 c. c. of nitric acid be added also the precipitate immediately dissolves completely. The remainder of the suspension is transferred to a porcelain dish and allowed to settle, decanted, and the precipitate washed twice with 50 c. c. of water. After the fluid has been poured off as completely as possible, the residue is evaporated to dryness on a water-bath, a small pinch of sulphuric anhydride is added and the mixture is heated over an open flame when it should immediately darken or char. By means of this test the presence of glycerophosphoric acid is proved with sufficient certainty; but if the absence of inorganic phosphorus compounds is to be shown also, the following reactions must be carried out in addition. If the aqueous solution of the glycerophosphate be added to an excess of ammonia (if necessary until the precipitate first formed is redissolved, as for example in the case of the zinc salt), the

addition of magnesia mixture should not cause immediate cloudiness (phosphates), nor should the addition of solution of silver nitrate, even with slight heating, cause darkening or charring (phosphides, phosphites, hypophosphites).

B. 2 grammes of the insoluble glycerophosphate or of the alkaloid-glycerophosphate are treated, heating if necessary, with a solution of 2 grammes of sodium carbonate in 100 c. c. of water, and filtered. The solution of sodium glycerophosphate thus obtained is neutralized with acetic acid and tested as explained above under A.

The tests for the salts of glycerophosphoric acid must be carried out according to the method already described for calcium and sodium glycerophosphate, taking into consideration the basic constituent and its characteristics.

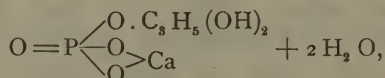
### Calcium Glycerophosphate.

As calcium glycerophosphate is both the most important and the most useful salt of glycerophosphoric acid, it shall be described first.

Glycerophosphoric acid is a dibasic acid and can therefore form acid and neutral salts. Accordingly I supply a neutral salt under the name of "neutral calcium glycerophosphate" and an acid salt under the name of "liquid calcium glycerophosphate".

### Neutral Calcium Glycerophosphate.

This salt, which fulfils the requirements of the Pharmacopœa Helvetica IV., and is also known under the name of "neurosin", forms a white, crystalline powder of the chemical formula



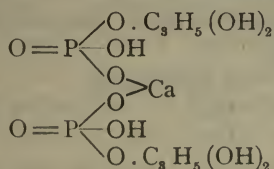
which dissolves in water at the ordinary temperature in the proportion of 1:40. This solution gives an alkaline reaction with litmus paper and becomes cloudy on heating, part of the salt being precipitated as such. On cooling the precipitate is completely redissolved. If a solution of lead acetate be added to the solution, a precipitate of lead glycerophosphate is formed, which dissolves with difficulty in acetic acid, but dissolves readily in nitric acid. The test for calcium glycerophosphate is carried out as follows:

A white precipitate is produced in the aqueous solution (1:40) both by a solution of lead acetate and by a solution of ammonium oxalate. When 25 c.c. of a solution of ammonium molybdate are added to the solution (1:40) at 15° C., a yellow precipitate should not be produced (phosphoric acid). When the solution (1:40) is acidified with nitric acid and solution of silver nitrate is added, it should not become definitely cloudy but merely opalescent (chlorides). If an excess of ammonia is added to this mixture and the latter is heated, it should not darken or char (phosphides, phosphites, hypophosphites). The solution of the calcium salt (1:40) should not be altered by sulphuretted hydrogen water (lead and other heavy metals). On ignition calcium glycerophosphate should leave 51 to 53 p. c. of ash.

For the quantitative estimation 1 gramme of calcium glycerophosphate is dissolved in 50 c.c. of water and titrated with normal hydrochloric acid solution, using methyl orange as an indicator. — 1 c.c. of normal hydrochloric acid corresponds to 0.071 gramme of  $P_2O_5$ , and 0.2461 gramme of calcium glycerophosphate ( $Ca PO_4 C_3 H_7 O_2 + 2H_2 O$ ). — If a little phenolphthalein solution be added to the solution which is neutral to methyl orange and this be titrated with normal potassium hydroxide solution, exactly the same amount of the latter should be required to turn the solution red as of normal hydrochloric acid solution used before.

#### Acid Calcium Glycerophosphate.

This preparation differs from the one just described in that it is hygroscopic, hence it is difficult to obtain in the solid state. For this reason the acid calcium glycerophosphate, which has the theoretical formula



can only be supplied in the form of a 50 p.c. solution. More concentrated solutions would be relatively much more expensive, and besides they are not sufficiently stable and have no practical advantage over the neutral calcium glycerophosphate, except that of solubility. The 50 p.c. solution is a

perfect substitute for the acid salt for therapeutic purposes, as long as it is given internally, but a solution of this kind is not suitable for subcutaneous use. I supply it under the name of "liquid calcium glycerophosphate 50 p. c.".

Besides the preparations already mentioned, I issue also a few specialities prepared from neutral calcium glycerophosphate and made to meet the special wishes of customers, such as

**Soluble Calcium Glycerophosphate,**  
the solubility of which is increased by the addition of a small quantity of citric acid, when it dissolves in water in the proportion 1:20,

**Granular Calcium Glycerophosphate**  
containing 95 p. c. of neutral calcium glycerophosphate.

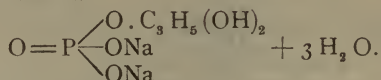
**Effervescent Granular Calcium Glycerophosphate,**  
a mixture of 30 p. c. of the neutral calcium salt with sodium bicarbonate and tartaric acid, which dissolves in water with the formation of carbonic acid gas, also

**Granular Calcium Glycerophosphate**  
containing 6 p. c., or 10 p. c., of calcium glycerophosphate, and finally

**Calcium Glycerophosphate Tablets,**  
each containing 0.1 gramme of neutral calcium glycerophosphate.

### **Sodium Glycerophosphate.**

The neutral sodium salt of glycerophosphoric acid has the chemical formula



**Crystalline Sodium Glycerophosphate,** and

**Powdered Sodium Glycerophosphate** 100 p. c., both correspond to the above formula and fulfil the requirements of the *Farmacopea ufficiale del regno d'Italia III.* as regards purity.

The crystalline salt forms white crystals, very readily soluble in water, corresponding to 70 p. c. of anhydrous  $\text{Na}_2\text{PO}_4\text{C}_3\text{H}_7\text{O}_2$ . The "powdered 100 p. c." is an extremely hygroscopic, white powder, which is also very readily soluble in water.

Sodium Glycerophosphate in dry pieces has the same constitution and is of equal purity.

The three varieties mentioned, which all represent 100 p. c.  $\text{Na}_2\text{PO}_4\text{C}_3\text{H}_7\text{O}_2 \cdot 3\text{H}_2\text{O}$ , are tested for purity and content in the following way:

The aqueous solution of sodium glycerophosphate gives an alkaline reaction with litmus. — The 5 p. c. aqueous solution is not altered by the addition of solution of calcium chloride at the ordinary temperature, but if heated to boiling point after the addition of solution of calcium chloride, a white precipitate is formed (calcium glycerophosphate), which redissolves as the mixture cools. — If dry sodium glycerophosphate be heated over an open flame, it chars. The ash left after complete ignition dissolves with effervescence in dilute nitric acid. If a solution of ammonium molybdate is added to the solution thus obtained, the well known phosphoric acid reaction (a yellow precipitate) is obtained in a short time, and more quickly on heating. The unaltered solution of sodium glycerophosphate should not give this reaction on the addition of the molybdate reagent at the ordinary temperature. But it occurs on boiling the mixture, as the glycerophosphoric acid is decomposed under these conditions with the formation of phosphoric acid. Unchanged glycerophosphoric acid does not react with ammonium molybdate, hence this reagent affords a useful means of detecting adulterations of the sodium glycerophosphate with sodium phosphate, or the recognition of a decomposed preparation. — 1 gramme of sodium glycerophosphate should yield a perfectly clear and colourless solution with 10 c. c. of water. — The aqueous solution (1:20), when acidulated with nitric acid, may become opalescent, but should not become definitely cloudy on the addition of solution of silver nitrate. Nor should dilute sulphuric acid cause a precipitate to form, even after standing for some time, and no change should occur on the addition of solution of sulphuretted hydrogen. After acidifying the solution with acetic acid, it should not

immediately become turbid on the addition of ammonium oxalate solution.

For the quantitative estimation of sodium glycerophosphate 1 gramme of the salt is dissolved in 50 c. c. of water and the solution titrated with normal hydrochloric acid solution, using methyl orange as indicator. 1 c.c. of normal hydrochloric acid solution corresponds to 0.071 gramme of  $P_2O_5$  or 0.27 gramme of  $Na_2PO_4 \cdot C_3H_7O_2 + 3H_2O$ . To the solution which is neutral to methyl orange phenolphthalein solution is now added, and the solution titrated with normal caustic soda solution. To turn the solution red the same quantity of normal caustic soda solution should be required as was used previously of normal hydrochloric acid solution.

Taking the content into consideration, the two following preparations can be tested in a similar way.

#### Sodium Glycerophosphate in 50 p. c. solution.

This is a colourless, or pale yellowish, syrupy liquid, which mixes with water in all proportions. It contains 50 p. c. of  $Na_2PO_4 \cdot C_3H_7O_2 + 3H_2O$ .

Sodium Glycerophosphate in 75 p.c. solution constitutes a clear, colourless, or pale yellowish, very viscous mass, soluble in water in all proportions and contains 75 p. c. of  $Na_2PO_4 \cdot C_3H_7O_2 + 3H_2O$ .

It has not been possible as yet to prepare an acid salt of glycerophosphoric acid corresponding to the formula  $NaHPO_4 \cdot C_3H_7O_2$  in a solid form, as all solid acid glycerophosphates decompose, or this occurs on further heating or evaporating. But a salt of this kind would be of no practical importance, as the neutral salt dissolves in water in all proportions. If any one should for any purpose require a highly concentrated solution of acid sodium glycerophosphate, he can use as a perfect substitute a solution of the pure 100 p. c. sodium glycerophosphate in ordinary commercial glycerophosphoric acid. If 40 grammes of sodium glycerophosphate are dissolved in 100 grammes of glycerophosphoric acid (25 p. c.), a 40 p. c. solution of  $NaHPO_4 \cdot C_3H_7O_2$  is obtained, which can be diluted with water as required. If 80 grammes of the sodium salt are dissolved in 100 grammes of 50 p. c. acid, a 63 p. c. solution of the acid salt is obtained.

**Ammonium Glycerophosphate.**

The only form in which I issue the ammonium salt of glycerophosphoric acid,  $(\text{NH}_4)_2\text{PO}_4\text{C}_3\text{H}_7\text{O}_2$ , is in a 50 p. c. solution. Thus it forms a colourless liquid, which mixes with water in all proportions.

**Bismuth Glycerophosphate**

is an insoluble, white powder, which on ignition leaves a residue of about 65 p. c. of bismuth oxide.

**Glycerophosphoric Acid.**

It is not possible to prepare a 100 p. c. glycerophosphoric acid, as the aqueous solution cannot be concentrated without decomposition. I supply a 25 p. c. and a 50 p. c. acid. They form colourless liquids, which are partially decomposed on heating and evaporating.

**Iron Glycerophosphate.**

I issue ferric glycerophosphate in the form of scales and powder. Both preparations dissolve in two parts of water and contain 14 to 15 p. c. of iron. I also supply liquid ferric glycerophosphate, a 50 p. c. aqueous solution of ferric glycerophosphate. In order to identify ferric glycerophosphate, a 5 p. c. aqueous solution of the salt is added to a solution of potassium ferrocyanide, the solution assumes a dark blue colour, and on the addition of hydrochloric acid a dark blue precipitate is formed. If a solution of lead acetate is added to the aqueous solution a light brown precipitate is immediately formed, which is readily soluble in nitric acid. When 0.2 gramme of ferric glycerophosphate is ignited and the resulting ash dissolved in 10 c. c. of hydrochloric acid (Sp. gr. 1.124) and the solution filtered, the addition of 25 c. c. of solution of ammonium molybdate should give in a short time the phosphoric acid reaction (yellow precipitate). If, however, a solution of 0.5 gramme of ferric glycerophosphate in 10 c. c. of water is added to 25 c. c. of solution of ammonium molybdate, only a very small amount of the yellow precipitate should be formed. On heating a solution of 1 gramme of ferric glycerophosphate in 20 c. c. of water with 10 c. c. of caustic soda solution (15 p. c.), and filtering, the filtrate, after being acidified with hydrochloric acid, should only become slightly

turbid on the addition of solution of barium chloride. When the residue left on the ignition of ferric glycerophosphate is moistened with water, it should not turn litmus paper blue.

For the quantitative estimation 1 gramme of the preparation is dissolved in 200 c.c. of water in a glass-stoppered bottle of 300 c.c. capacity; 5 grammes of potassium iodide and 15 c.c. of hydrochloric acid (sp. gr. 1.124) are added, and the mixture is left to stand for an hour in the closed bottle at the temperature of the room. Thereupon 30 c.c. of  $\frac{1}{10}$  normal sodium thiosulphate solution are added, and after the addition of starch solution, this is titrated with  $\frac{1}{10}$  normal iodine solution. 1 c.c. of the  $\frac{1}{10}$  normal sodium thiosulphate solution corresponds to 0.0056 gramme of iron.

Besides the salts of glycerophosphoric acid already described, the following may be considered.

### **Lithium Glycerophosphate.**

Lithium glycerophosphate,  $\text{Li}_2\text{PO}_4\text{C}_3\text{H}_7\text{O}_2$ , is a white powder readily soluble in water. It can be tested in a similar way to the sodium salt.

### **Manganese Glycerophosphate.**

Neutral manganese glycerophosphate is a reddish-white salt, soluble in water with great difficulty.

Soluble manganese glycerophosphate is an acid salt, soluble in water. It too is a reddish-white powder.

### **Magnesium Glycerophosphate.**

Magnesium glycerophosphate is a white powder, readily soluble in water. In a 50 p.c. solution it is a colourless or pale yellowish liquid.

### **Potassium Glycerophosphate.**

The 100 p.c. potassium glycerophosphate,  $\text{K}_2\text{PO}_4\text{C}_3\text{H}_7\text{O}_2 + 3\text{H}_2\text{O}$ , forms a pale yellowish, dough-like mass, soluble in water in all proportions. The 50 p.c. and 75 p.c. solutions of the potassium salt are colourless or pale yellowish, syrupy liquids. These three preparations,

Potassium glycerophosphate 100 p.c.,

Potassium glycerophosphate 75 p.c. and,

Potassium glycerophosphate 50 p.c.

can be tested for purity in the same way as described under sodium glycerophosphate. For the quantitative estimation it should be noted, that, according to the method of titration indicated, 1 c. c. of normal hydrochloric acid corresponds to 0.071 gramme of  $P_2O_5$ , and 0.302 gramme of  $K_2PO_4$   $C_3H_7O_2 + 3H_2O$ .

#### **Quinine Glycerophosphate.**

Quinine glycerophosphate,  $H_2PO_4 C_3H_7O_2 (C_{20}H_{24}O_2N_2)_2 + 4H_2O$ , is a white powder, soluble in hot water and in alcohol; it contains about 72 p. c. of quinine. In aqueous solution it combines with ferric glycerophosphate, but the neutral sodium and calcium glycerophosphates cause the quinine to separate out. Consequently a combination of this sort is only possible when the solutions of the above salts in water are first rendered slightly acid with glycerophosphoric acid.

#### **Strontium Glycerophosphate.**

Neutral strontium glycerophosphate,  $SrPO_4 C_3H_7O_2$ , is a white powder, sparingly soluble in water.

#### **Strychnine Glycerophosphate.**

Strychnine glycerophosphate is a white, crystalline powder, soluble in water. In aqueous solution it reacts in the same way as quinine glycerophosphate with the other salts of glycerophosphoric acid.

#### **Zinc Glycerophosphate.**

Zinc glycerophosphate,  $ZnPO_4 C_3H_7O_2$ , is a white powder, soluble in water. In aqueous solution it is not precipitated by the other water-soluble salts of glycerophosphoric acid, and can therefore be combined with these when required.

### **Part II. Medical.**

Phosphorus and its compounds form an essential part of all organic life. Plants require phosphates from the earliest period of their germination, and seeds contain a plentiful supply of these salts. Phosphorus compounds are contained in every vegetable cell. These enter the animal and human organism in their vegetable food, and there in the form of

nuclein, lecithin, cerebrin, the phosphoric acid of meat, etc., they play an important part in the life of the cell and of the entire organism. When these substances are split up, the phosphorus appears in the urine in the form of alkaline and earthy phosphates. It is well known that it was first prepared from urine by Brand (1669), Kunkel (1678), and Krafft (1667). Later, Lavoisier (1772) recognised its elementary character and described its property of combining with oxygen to form phosphoric acid. When the identity of phosphoric acid and its salts became known, their importance in the physiology of plant and animal life was soon recognised. The bones especially were found to be very rich in phosphates. At the present time, besides the phosphates occurring in the mineral kingdom (apatite, phosphorite, wavellite, meadow-ore, and others) the bones of animals constitute the chief source for the technical extraction of phosphorus. How rich the bones are in phosphoric acid is apparent when we consider that the skeleton of an adult yields 1200 to 1500 grammes of phosphoric acid; this is present in the bones in the form of the tri-calcium phosphate.

The importance of the metabolism of phosphoric acid was first recognised by the constant presence of phosphoric acid salts in the urine. A normal adult excretes 3 to 4 grammes of phosphoric acid in the urine daily. This is chiefly derived from the vegetable food, and is partly a product of decomposition of nuclein and lecithin. Such decomposition is said to occur, for example, as a result of muscular exercise, as stated by Mosler and Lehmann.

Others assume that phosphoric acid is also liberated from its organic combination by increased nervous exertion. Thus Mairet regards the alkaline phosphates present in the circulation as a product of cerebral activity; this might be possible considering the high proportion of lecithin contained in the brain, but would be difficult to demonstrate. Mairet's view agrees with the findings of Mendel, Vanni and Pons, in that these investigators noticed a diminution in the excretion of phosphoric acid in those suffering from chronic brain dis-

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Mosler, Beiträge zur Kenntniss der Urinabsonderung. Gießen 1853.

Lehmann, Archiv für Anatomie und Physiologie 1871, p. 14.

Mairet, Comptes rendus de l'académie des sciences, Vol. 99, p. 282.

Mendel, Archiv für Psychiatrie 1872, p. 636.

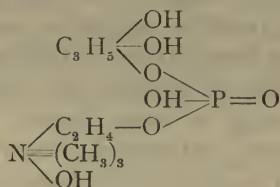
Vanni-Pons, Annali di chimica e di farmacologia 1887, p. 259.

ease. A diminution in the excretion of phosphoric acid was also found to occur in other diseases, such as arthritis, diabetes, acute atrophy of the liver, renal disease, acute infective diseases, etc. Its usual occurrence in pregnancy is easily explained by the fact that the foetus requires a large amount of phosphates for the formation of its bones. The excretion of phosphoric acid may also be increased, an occurrence known as phosphaturia; the cause may be found in digestive disturbances, fatigue, recent fever, nervousness, softening of the bones, etc. In cases of this kind the amount of phosphoric acid contained in the urine may be increased up to 9 grammes a day.

As regards the therapeutic use of phosphoric acid and its salts, this can be traced back far beyond the period when phosphorus was discovered, and the origin of its administration in the form of bone-ash cannot be stated with certainty. Phosphates were certainly used empirically in therapeutics at an early period. After the phosphates had been discovered with the help of chemistry, and their use in the economy of the organism made manifest with the aid of physiology, the pure salts of phosphorus were more used, and later the element phosphorus itself. But after a time it was observed that the inorganic compounds of phosphoric acid had a relatively small influence on phosphoric acid metabolism; this is due chiefly to the slight extent to which they are absorbed and made use of by the organism. If, for instance, sodium phosphate is injected subcutaneously or intravenously, the whole of it will appear in the urine in a short time. Sodium phosphate is of limited use internally, as it practically only displays the purgative action of sodium sulphate and is absolutely useless in the chief indications for phosphorus therapy (rickets, scrofula, and diabetes). Theoretical considerations have proved a failure in this connection. But the administration of phosphorus itself has attained significance, not so much in skin disease, heart disease, impotence, angina pectoris and neuralgia, as in rickets. There are some, however, who consider phosphorus of little or no value in rickets. And it is also noteworthy that bone formation is little influenced by phosphorus, while nervous symptoms and the general state of health are affected to a much greater extent. It cannot, therefore, be considered absurd to deny that phosphorus has any direct influence on phos-

phate metabolism. How, indeed, could it be expected to act? In the form of an element an action would be contrary to the chemical properties of phosphorus, and oxidised, as phosphoric acid, it has no value. Either then a selective action on the cells must be attributed to it, or it must be supposed to be comparable to arsenic in its method of action. It is well known that treatment by arsenic greatly benefits the general health and improves nervous symptoms. Hence if the administration of phosphorus has occasionally been observed to have a favourable influence on the bony structure, its action may quite well be secondary, i. e., a consequence of the improvement in the general health. There is as yet no evidence, either physiological or pharmacological, that phosphorus has a directly favourable influence on bone formation, nor has this been found to be the case in practice. What object then could there be in clinging to such a method of treatment, which besides is not without danger? Deeper penetration into the physiology of metabolism and its products showed us a safer method of procedure.

Shortly after the discovery of glycerophosphoric acid by Pelouze, Gobley, as has been mentioned above, demonstrated the presence of glycerophosphoric acid in a fatty substance which Vauquelin (1811) had already prepared from yolk of egg. He obtained it by treating Vauquelin's substance, which he called lecithin, with caustic potash, whereby potassium glycerophosphate was separated. Strecker examined more minutely the chemical procedure by which lecithin was split off. He found, as Diakonow had done before, that in lecithin the glycerophosphoric acid is bound to choline. According to this the theoretical lecithin would have the constitutional formula:



However, in the lecithins which occur naturally the two free hydroxyl groups, or the hydrogen atoms be-

Strecker, Liebig's Annalen 1868, Vol. 147, p. 77.

Diakonow, Zentralblatt für die medizinischen Wissenschaften 1868, No. 1 and 7.

longing to the glycerin radical are replaced by the acid residues of palmitic acid ( $-C_{16}H_{31}O$ ), stearic acid ( $-C_{18}H_{35}O$ ) or oleic acid ( $-C_{18}H_{33}O$ ). Therefore, in the saponification of the lecithins, besides choline and glycerophosphoric acid, the soaps of the fatty acids just mentioned are also formed. A similar process is caused, according to Bókay, by the fat-splitting ferment of the pancreas or the putrefactive ferment in the gut. The products of decomposition (choline, glycerophosphoric acid, and fatty acids) are absorbed from the intestine and carried to the circulation. This can easily be demonstrated after consuming lecithin by the increase in the phosphoric acid metabolism or the increased excretion of phosphoric acid in the urine. According to Sotnitschewsky, the presence of glycerophosphoric acid can also be demonstrated in the urine, though Robin threw doubt on this observation. He believes, probably correctly, that glycerophosphoric acid is not present as such in the urine, but is formed from the lecithin in the urine by the chemical reaction of the reagents used for testing the urine. The presence of glycerophosphoric acid in wine observed by Funaro and Rastelli and its presence in cod-liver oil, confirmed by Gautier and Morgues, might in the same way be traced to the presence of lecithin, which is a constituent of all vegetable and animal tissues.

The communication of G. de Pasqualis forms an important supplement to the work of Bókay. This observer not only confirmed the view that lecithin, during the process of digestion, was split up into choline and glycerophosphoric acid, but also showed that glycerophosphoric acid or its salts represent the form of phosphorus which occurs as the product of metabolism, and is the most suitable for absorption into the body. Thus the path was found which should be followed in the treatment of disturbances of phosphate metabolism, and from this time on the glycerophosphates have become established in our materia medica

Bókay, Zeitschrift für physiologische Chemie 1877, Vol. 1, p. 157.

Sotnitschewsky, Zeitschrift für physiolog. Chemie, Vol. 4, p. 214.

Robin, Archives de pharmacie, Vol. 2, p. 532.

Funaro-Rastelli, Stazione sperimentale agraria italiana, Vol. 39, p. 35.

Gautier-Morgues, Bulletin de la société chimique (3), Vol. 2, p. 213.

Pasqualis, Annali di chimica e di farmacologia 1893, p. 137.

and have been regarded with increasing favour. This was facilitated by the fact that they are absolutely harmless to the human body even in large doses, and yet fulfil their object in small doses.

The works of Pasqualis, K. Bülow, A. Robin, E. Delage, and A. Marua y Valerdi must also be considered in reviewing the physiology of glycerophosphoric acid. According to these authors, glycerophosphoric acid is digested without any difficulty by the stomach or intestines, it is quickly absorbed and reaches the circulation unaltered. Later it is found in the urine in the form of phosphoric acid salts. Robin, to whose work the introduction of the glycerophosphates into therapeutics is greatly due, gave as his opinion, as the result of his studies, that the glycerophosphates exercise a selective action on the nutrition of the nerves, and he thus encouraged their use as a nerve tonic. From his publications on this subject it appears also that the introduction of glycerophosphates into the body increases general metabolism, and has a specially favourable influence on the exchange of nitrogen. Besides this they are said to assist the more complete utilisation of sulphur compounds in the body. Further, the assimilation of nutritive phosphates by the nerves is promoted and excretion modified in the nervous system. Thus the glycerophosphates may be considered a direct means of sparing the nervous system. Finally Robin points out that calcium metabolism is greatly stimulated by the glycerophosphates, especially in bone substance, but the phosphorus exchange in the bone tissue remains uninfluenced.

The most important glycerophosphates for therapeutic use are the sodium, calcium and iron salts of glycerophosphoric acid; they shall therefore be discussed first. Free glycerophosphoric acid is of little value therapeutically. It serves principally as an addition to solutions of glycerophosphates, when these for any reason are required to give an acid reaction.

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Pasqualis, *Annali di chimica e di farmacologia* 1894, p. 154.

Bülow, *Archiv für Physiologie* 1894, p. 89.

Robin, *Nouveaux remèdes* 1894, p. 203. *Répertoire de pharmacie* 1895, p. 308.

Delage, *Thèse de Paris* 1896.

Valerdi, *Monitor de Farmacia y de la Terapia* 1896, No. 43.

### Sodium Glycerophosphate.

Of the preparations mentioned on page 8 all are suitable for internal use; for purely physical reasons crystalline sodium glycerophosphate and its 50 p. c., or 75 p. c., solutions are best suited for subcutaneous and intravenous injection. As solutions of sodium glycerophosphate in water are not decomposed at 100° to 120° C., nothing stands in the way of their sterilisation for subcutaneous and intravenous use. Sodium chloride and other glycerophosphates, such as the iron and quinine salts, may also be added; but care is necessary in the case of other salts, as they may in certain cases cause decomposition at the ordinary temperature or on heating, as for example sodium phosphate, mineral acids, carbonates and lead salts. The dosage of sodium glycerophosphate, about to be described, refers to the 100 p. c. salt having the formula  $\text{Na}_2\text{PO}_4 \cdot \text{C}_3\text{H}_7\text{O}_2 + 3\text{H}_2\text{O}$ . Thus, for example, when using the 50 p. c. solution as supplied by me (sodium glycerophosphate 50 p. c.), a double dose would be required.

Robin first recommended sodium glycerophosphate as a nerve tonic to be given by mouth and subcutaneously and obtained most excellent results in convalescence from influenza and other infective diseases, and also in nervous asthenia of any origin, such as sciatica, tic douloureux, and furthermore in Addison's disease, lumbago, Graves' disease, and phosphaturia. The remedy is less effective in tabes dorsalis, in which its action seems restricted to the diminution of the lightning pains. In a case of facial neuralgia described by Robin, sodium glycerophosphate had an excellent result. After the author had used osmic acid and other medications without benefit, he injected a 25 p. c. aqueous solution of sodium glycerophosphate directly into the nerve or its immediate neighbourhood, with the result that a noticeable improvement occurred, and with daily repetition of the injection the patient was again able to sleep.

Sodium glycerophosphate is very serviceable in sciatica, as is stated by Robin and confirmed by Billard. A subcutaneous injection of 1 c. c. (17 min.) of the 25 p. c. solution is given first and this dose gradually increased to 2 to 4 c. c.

Robin, *Journal des praticiens* 1906, p. 409.

Robin, *Bulletin général de thérapeutique* 1897, 30<sup>th</sup> May.

Billard, *Medical News of the American Medical and Surgical Bulletin* 1897, p. 166.

(34—68 min.). But for ordinary purposes a dose of 2 c. c. (34 min.) is sufficient. The injection itself is given very slowly and as deep as possible into the muscular tissue and in the immediate neighbourhood of the nerve. By taking full aseptic precautions these injections cause neither pain nor inflammation. The improvement usually sets in very quickly, but only becomes definite by prolonged use of the injections. By means of this treatment, which is quite free from danger, out of 63 cases, Robin succeeded in achieving a cure in 41 and a more or less definite improvement in 18. In 4 cases only was the treatment unsuccessful.

Sodium glycerophosphate is also useful, according to Robin, in the treatment of lumbago. He recommended it chiefly in those cases which did not appear suitable for the use of jaborandi, and he succeeded in causing the disappearance of the motor disturbances within a few days. As a daily dose he suggests 0.3—0.5 gramme (5 to  $7\frac{1}{2}$  grains) of the salt, administered subcutaneously into the lumbar region.

The internal administration of sodium glycerophosphate also often shows good results. Starr had satisfactory results with the use of this medicament in Graves' disease. In one case, in which a variety of remedies had been tried for  $1\frac{1}{2}$  years without success, he succeeded in bringing about a decided improvement in a fortnight. His prescription was:

Rp. Sodii glycerophos.	25.0 grammes ( $\frac{5}{6}$ oz)
Aq. destill.	25.0 grammes ( $\frac{5}{6}$ oz)
Aq. aurant. flor.	55.0 grammes ( $1\frac{5}{6}$ oz)
Syrup. aurant. cort.	20.0 grammes ( $\frac{2}{3}$ oz)

Sig. One teaspoonful to be taken 3—4 times daily.

Kahane, as the result of many trials, confirmed the value of sodium glycerophosphate when used internally in Graves' disease, and recommends it also in the treatment of chronic myelitis, hysteria, neurasthenia and neuroses. According to T. Harris, its use should also be seriously considered in the treatment of nervous exhaustion following mental strain. Kahane prescribed the glycerophosphate, which in his experience never gave rise to unpleasant effects, in spite of its action in strengthening and improving the health, as follows:

Starr, Medical News 1896, 18th April.

Kahane, Nouveaux remèdes 1899, p. 301.

Harris, British Medical Journal 1899, No. 2033, p. 1681.

- Rp. Sodii glycerophos.      25.0 grammes ( $\frac{5}{6}$  oz)  
Aq. destill.  
Aq. aurant. flor.      50.0 grammes ( $1\frac{2}{3}$  oz)  
Syrup. aurant. cort.      20.0 grammes ( $\frac{2}{3}$  oz)  
Sig. One teaspoonful to be taken three times daily.

G. Bardet gave as his opinion that the action of the acid salts of glycerophosphoric acid was stronger, but that these were only suited for internal use. He also mentioned an acid sodium glycerophosphate. As it has not been possible as yet to prepare this salt, a mixture of sodium glycerophosphate and glycerophosphoric acid in molecular proportions was probably meant, and it is certain that Bardet possessed nothing but this for his experiments. The author states that this mixture, given in daily doses of 15 to 25 grammes ( $1\frac{1}{2}$ — $\frac{5}{6}$  oz) has besides its specific action also a mild purgative effect which could be used for therapeutic purposes. The mechanism of this action is said to be similar to that of tribasic sodium phosphate and only to differ from the latter in its strong action as a cholagogue. This makes the preparation suitable for the treatment of dyspepsia, hyperchlorhydria, habitual constipation, and sluggish liver.

Generally speaking the following indications for sodium glycerophosphate may be given: diminution in general metabolism and in lime metabolism in the bones, disturbances in phosphate metabolism, progressive paralysis, senility, tabes dorsalis, diabetes, scrofula, rickets, neuroses, neurasthenia, neuralgia, lumbago, sciatica, tic douloureux, nerve atrophy, nerve weakness, hysteria, Addison's disease, Graves' disease, chronic myelitis, atrophy of the liver, sluggish liver, constipation, dyspepsia, hyperchlorhydria, phosphaturia, mental and physical overwork, and convalescence from debilitating infective diseases.

The dosage and method of administration of sodium glycerophosphate must vary according to the form of disease and the physical condition of the patient. In those cases not requiring rapid or local action, as for example sciatica and facial neuralgia, internal treatment will generally be adopted, as it is more agreeable to the patient. The prepa-

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Bardet, Nouveaux remèdes 1900, p. 169. — Comptes rendus de l'académie des sciences, Vol. 130, p. 956.

ration is then given in the form of powders, pills or mixtures. If a prolonged course of glycerophosphate is necessary, as for instance in weakly children, the preparation may be given in the food or with children's food, rusks, etc. Southern wines also form a useful excipient for glycerophosphate for general and constant use. Aqueous solutions are less suited unless they are used up in a few days, as glycerophosphates in aqueous solution constitute a good culture media for fungi and bacteria and hence do not keep well in this form. For the same reason solutions destined for subcutaneous injection must always be sterilised before use. They are therefore prescribed thus:

Rp. Sodii glycerophos. 1.0 gramme (15 grains)  
Sodii chlor. 0.03 gramme ( $\frac{1}{2}$  grain)  
Aq. destill. ad 5.0 grammes (85 min.)

To be sterilised. For subcutaneous (intramuscular) injection. 1 c. c. (17 min.) to be given once or twice daily.

Naturally sterile solutions of this kind can be used after adequate dilution for intravenous infusion.

There is no need to be too cautious in the internal administration of sodium glycerophosphate, as it is perfectly harmless. For economic reasons it is best to keep to the small doses generally used, so long as there is no proof that larger doses have a better and more rapid action. For adults single doses of 1 to 2 grammes (15—30 grains), and daily doses of 5 to 10 grammes (75—150 grains) are prescribed. Very young children can take 0.2 to 0.5 gramme ( $3-7\frac{1}{2}$  grains) daily, and older children 1 to 5 grammes (15—75 grains). Larger doses are only necessary for adults when the cholagogue action of the drug is sought.

### Calcium Glycerophosphate.

Robin and Pasqualis were the first to describe the therapeutic use of calcium glycerophosphate. The latter author pointed out that the action of calcium phosphate and of calcium glycerophosphate differed both physiologically and pharmacologically. Thus the excretion of phosphoric acid with constant

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Robin, Gazette médicale de Paris 1894, p. 193. — Bulletin général de thérapeutique 1895, p. 385 and 433.

Pasqualis, Annali di chimica e di farmacologia 1894, p. 94 and 145.

diet is increased in the first 24 hours when calcium glycerophosphate is administered, whereas with calcium phosphate an increase in phosphate metabolism can only be recognised after 2 days. The explanation of this observation is that glycerophosphate is much more readily absorbed and utilised by the organism than is the phosphate. Even with large doses of calcium glycerophosphate Pasqualis could only find traces of glycerophosphoric acid in the urine, and these might, as I have already pointed out, be due to alteration in the lecithin normally present in urine. The complete utilisation of glycerophosphoric acid by the organism is the explanation why comparatively small doses usually suffice. According to Robin, calcium glycerophosphate not only increases phosphate metabolism, but it also increases the solid constituents of the urine, as for example the urea content rises from 23 p. c. to 32 p. c., and of the chlorides and sulphates, and further the oxidation of nitrogen from 87 p. c. to 90 p. c. But uric acid excretion, according to the author, is not influenced. He concludes that the use of glycerophosphate is only indicated in those diseases in which a diminution in the exchange of nitrogen and sulphur can be demonstrated. He considers calcium glycerophosphate specially suitable in conditions of depression in patients suffering from phosphaturia, in convalescence from influenza, and other infective diseases, in neurasthenia, in torpid chlorosis with diminished nitrogen exchange, in phosphaturia either with or without albuminuria, in rickets, Addison's disease, sciatica, facial neuralgia, scrofula and tabes dorsalis. He considers the subcutaneous administration of the preparation to be more effective as a rule, but he also obtained satisfactory results by prescribing it internally. Subcutaneously he gives daily doses of 0.05 to 0.5 gramme ( $\frac{3}{4}$ — $7\frac{1}{2}$  grains) and internally daily doses beginning with 0.5 to 1 gramme ( $7\frac{1}{2}$ —15 grains). In phosphaturia he prescribes for example:

Rp. Calcii glycerophosph.	0.2—0.4 gramme (3—6 grains)
Nuc. vomic. pulv.	0.02—0.03 gramme ( $\frac{1}{3}$ — $\frac{1}{2}$ grain)
Albuminis ovi siccati	0.1 gramme ( $1\frac{1}{2}$ grains)

Ft. pulv. Mitte X. Sig. One powder to be taken at each meal.

Gay prescribed calcium glycerophosphate as follows:

Rp. Calcii glycerophosph. 10.0 grammes ( $\frac{1}{3}$  oz)  
 Acid. citric. 1.0 gramme (15 grains)  
 Sacchar. 610.0 grammes ( $20\frac{1}{3}$  oz)  
 Aq. destill. 340.0 grammes ( $11\frac{1}{3}$  oz)  
 Solve agitando neve calorem adhibendo et adde  
 Syrup. aurant. cort. q.s. ad 1000.0 grammes ( $33\frac{1}{3}$  oz).  
 Sig. One tablespoonful to be taken thrice daily.  
 (Not suitable for keeping long.)

Rp. Calcii glycerophosph. 0.15—0.3 gramme ( $2\frac{1}{2}$ —5 grains)  
 Massae cacao 0.1 gramme ( $1\frac{1}{2}$  grains)  
 Fiat. pastill. Mitte 50. S. 1 pastille 4 times daily.  
 (Pastilles containing 0.1 gramme ( $1\frac{1}{2}$  grains)  
 are manufactured).

Rp. Calcii glycerophosph. 1.0—3.0 grammes (15—45 grains)  
 Acid. citric. 0.1—0.3 gramme ( $1\frac{1}{2}$ —5 grains)  
 Aq. destill. 100.0 grammes ( $3\frac{1}{3}$  oz)  
 Sig. One tablespoonful to be taken several times a day.

Carles has given the following prescription for the preparation of a wine containing calcium glycerophosphate:

Rp. Calcii glycerophosph. neutral. 10.0 grammes ( $\frac{1}{3}$  oz)  
 Vin. Xerensis 750.0 grammes (25 oz)  
 adde  
 Acid. tartar. 3.0 grammes (45 grains)  
 Vin. Xerensis 250.0 grammes ( $8\frac{1}{3}$  oz)

It may be noted that Gay also prescribed calcium glycerophosphate in effervescing mixtures, prepared by adding a suitable amount of sodium bicarbonate and citric acid to the aqueous solution. But granular effervescent calcium glycerophosphate is a much more convenient form, as it dissolves in water with effervescence. A fairly large pinch of this preparation is taken in a glass of water several times daily.

Patin gives incontinence of urine as another indication for calcium glycerophosphate. On account of its harmlessness it can be safely given to children as well as to adults. For adults 2 daily doses of 0.5 gramme ( $7\frac{1}{2}$  grains) each suffice, and for children, according to their age, a dose of 0.25—0.4 gramme (4—6 grains), morning and evening.

In influenza calcium glycerophosphate with quinine has proved very useful. Capitan recommends it in the following form:

Rp. Calcii glycerophosph.

Quinin. hydrobrom. aa 0.5 gramme ( $7\frac{1}{2}$  grains)

M. Mitte X.

Sig. 1—2 powders to be taken daily.

Jaquet obtained a good result in alopecia areata by giving 0.15 gramme ( $2\frac{1}{2}$  grains) of the preparation after every meal, besides continuing the local treatment. It may also be given alternately with sodium monomethylarsenate, as was suggested by Brocq. In this case a small teaspoonful of a solution of 0.5 gramme ( $7\frac{1}{2}$  grains) of sodium monomethylarsenate in 175 grammes ( $5\frac{5}{6}$  oz) of water and 25 grammes ( $\frac{5}{6}$  oz) of aqua laurocerasi is given after every meal for a fortnight, and then for the next fortnight this medicine is replaced by the following powders:

Rp. Calcii glycerophosph. 0.25 gramme (4 grains)

Magnesii glycerophosph. 0.1 gramme ( $1\frac{1}{2}$  grains)

Sodii phosph. 0.25 gramme (4 grains)

Maltine 0.03 gramme ( $\frac{1}{2}$  grain)

Quassin 0.01 gramme ( $\frac{1}{6}$  grain)

Ft. pulv. Mitte XXVIII. Sig. 2 powders daily.

Calcium glycerophosphate also deserves due consideration in the treatment of pulmonary tuberculosis. Michelozzi and Angiulli have tested its value both pharmacologically and clinically. Michelozzi gave infected rabbits daily doses of 3 grammes and obtained clinical and structural cures. Angiulli prescribed it in human practice both internally and subcutaneously with very good results. The ingestion of calcium salts is necessary, in his experience, because the excretion of calcium is increased in tuberculosis, thus causing poverty of calcium salts in the body; also the impregnation of the tuberculous focus with calcium salts may initiate or hasten the healing process. Therefore 0.5 gramme ( $7\frac{1}{2}$  grains) of calcium glycerophosphate are given internally 3—4 times a day, or 2—5 c.c. (34—85 min.) of a 20 p.c.

Capitan, *Médecine moderne* 1905, 7<sup>th</sup> March. — *Revue de thérapeutique* 1905, p. 160.

Jaquet, *Journal médical de Bruxelles* 1905, p. 141.

Brocq, *Journal médical de Bruxelles* 1905, p. 141.

Michelozzi, Angiulli, *Il Morgagni* 1906, No. 21.

solution are injected daily subcutaneously. The author brought about a cure on an average by means of 90 injections. These were always well borne and markedly contributed to the improvement in the clinical signs. But Angiulli also records direct cures in patients in the first and second stages of the disease. If Mitilescu believes that the increased excretion of phosphoric acid which follows the ingestion of the glycerophosphate proves that the calcium is not retained and only acts by stimulating metabolism, his view is contradicted both by Angiulli's successful results and by Tunicliffe's observations. The latter showed that in spite of the increased excretion of phosphoric acid by the organism, phosphorus was also retained in greater quantities if calcium glycerophosphate were added to the food. Calcium phosphate does not act in this way; nor can it, like calcium glycerophosphate, increase the assimilation of nitrogen from the food.

P. Sittler states that calcium glycerophosphate is useful in rickets, when combined with sodium nucleinate. He prescribed these medicaments in the form of powders or tablets. According to the age of the child, sodium nucleinate is given in daily doses of 0.2—0.5 gramme (3—7½ grains), and calcium glycerophosphate in daily doses of 0.1—0.25 gramme (1½—4 grains).

In conditions of general weakness, *dentitio difficilis*, chlorosis, anæmia and for convalescents, Dujardin-Baumetz's prescription can be recommended:

Rp. Calcii glycerophosph.	5.0 grammes (75 grains)
Vin. cinchon.	200.0 grammes (6⅔ oz)
Vin. kolæ	200.0 grammes (6⅔ oz)
Syrup. aurant. cort.	50.0 grammes (1⅔ oz)

Sig. One liqueurglass full to be taken with meals.

A calcium syrup which is pleasant to the taste and keeps well is obtained by dissolving 10 grammes of neutral or acid calcium glycerophosphate in 900 grammes of syrup and adding 100 grammes of syrup. aurant. cort., or syrup. aurant. flor. Of this syrup children may take a teaspoonful to

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Mitilescu, Spitalul, 1906, No. 1. — Zeitschrift für Tuberkulose und Heilstättenwesen 1906, No. 1.

Tunicliffe, Archives internationales de pharmacodynamie et de thérapie, Vol. 16, p. 207.

Sittler, Münchener medizinische Wochenschrift 1907, p. 1437.

a tablespoonful, according to their age, once or several times daily.

Calcium glycerophosphate being the most harmless and effective nerve tonic it has been widely used. Like other glycerophosphates it has been especially employed in the form of medicated wines, for the nutrition of children and as a general strengthening medicine; thus it forms the principal ingredient of antisclerosin, which is much used in arteriosclerosis.

The indications for calcium glycerophosphate are: General conditions of debility, especially after infective diseases, senility, arteriosclerosis, Addison's disease, phosphaturia, influenza, tuberculosis, anæmia, chlorosis, incontinence of urine, nocturnal enuresis of infants, tabes dorsalis, rickets, osteomalacia, scrofula, nerve atrophy, nervous debility, neurasthenia, hysteria, sciatica, facial neuralgia, over exertion, convalescence, and alopecia areata.

The dosage for subcutaneous injection is usually 0.2—0.5 gramme ( $3-7\frac{1}{2}$  grains) in aqueous solution or suspension once daily. The preparation is not decomposed when sterilised in aqueous solution; I would point out, however, that solutions of calcium glycerophosphate become cloudy on heating, part of the salt being precipitated. On cooling it is redissolved. Calcium glycerophosphate is given internally to adults in single doses of 0.2—0.5 gramme ( $3-7\frac{1}{2}$  grains) and in daily doses up to 10 grammes ( $\frac{1}{3}$  oz); to children, according to their age, in daily doses of 0.3—3 grammes (5—45 grains).

#### Ferric Glycerophosphate.

As calcium glycerophosphate has won so much appreciation in the treatment of chlorosis, anæmia and debilitating diseases on account of the favourable influence it exerts on metabolism, with consequent improvement in the general physical condition, an even more favourable action might be expected from the glycerophosphate of iron. And indeed this preparation has become one of the most popular of the glycerophosphates, as well as of the iron compounds. The preparation is distinguished from most of the usual iron compounds by its ready absorption and rapid action, and it is therefore regarded with increasing favour in the treat-

ment of the diseases above named. Robin had already recognised the good qualities of iron glycerophosphate and had prescribed it with marked benefit. He gave it in the form of pills or syrup, and in combination with kola and nux vomica in daily doses of 0.3 gramme (5 grains).

Bardet and Gay have expressed very favourable opinions as to the value of ferric glycerophosphate in the treatment of anæmia and chlorosis. It is also frequently used as a tonic for weakly and ill-nourished persons, and in neurasthenia, phosphaturia, and Graves' disease. The following prescriptions can be recommended:

Rp. Ferri glycerophosph. 10.0 grammes ( $\frac{1}{3}$  oz)  
Misce terendo cum  
Glycerin. puriss. 40.0—50.0 grammes ( $1\frac{1}{8}$  oz)  
adde

Vini Hispanici albi 1000.0 grammes ( $33\frac{1}{3}$  oz)

Digere per horas IV interdum agitando, deinde filtra.

Sig. Tonic wine. A liqueurglass full before each meal.

Rp. Ferri glycerophosph. 1.5—3.0 grammes (24—45 grains)  
Rad. rhei pulv. 1.5—3.0 grammes (24—45 grains)  
Extract. cinchon. regiæ 4.5—3.0 grammes (68—45 grains)  
M. Ft. pil. 60. Consperge cort. cinnam. pulv.

Sig. 4—6 pills to be taken daily with meals.

Rp. Ferri glycerophosph. 2.0 grammes (30 grains)  
Aq. cinnam. 40.0 grammes ( $1\frac{1}{3}$  oz)  
Syrup. aurant. cort. ad 200.0 grammes ( $6\frac{2}{3}$  oz)

Sig. One tablespoonful in a glass of water several times daily. (Liebreich—Langgaard.)

Granular Ferric Glycerophosphate (containing 10 p. c. of ferric glycerophosphate) is another convenient form in which the salt may be administered. It may be prescribed in the form of powder, of which a pinch is taken in water or wine several times daily after meals. The other two preparations mentioned on page 9 are alike both as regards constitution and practical use; their external appearance is varied to suit the wishes and tastes of customers. As both consist of pure ferric glycerophosphate, the doses mentioned above and in the following also apply to them.

**Indications:** Debilitating diseases, convalescence, neurasthenia, anæmia, chlorosis, influenza, beri-beri, Addison's disease, Graves' disease, phosphaturia.

**Dosage:** Internally, for adults, usually single doses of 0.1—0.2 gramme ( $1\frac{1}{2}$ —3 grains), and daily doses of 0.3 to 0.6 gramme (5—10 grains) or more; for children, according to their age, daily doses of 0.05—0.2 gramme ( $\frac{3}{4}$ —3 grains). Iron glycerophosphate may also be given to adults subcutaneously in sterile aqueous solution in doses of 0.1 gramme ( $1\frac{1}{2}$  grains).

### Potassium Glycerophosphate.

Potassium glycerophosphate may be given by itself or mixed with other glycerophosphates in the same doses and for the same diseases as the sodium salt. It has also been given subcutaneously, prescribed as follows:

Rp. Potassii glycerophosph.	1.0 gramme (15 grains)
Sod. chlor.	0.03 gramme ( $\frac{1}{2}$ grain)
Aq. destill.	5.0 grammes (85 min.)

To be sterilised.

Sig. 1 c. c. (17 min.) to be injected daily.

### Lithium Glycerophosphate.

The therapeutic use of lithium glycerophosphate is indicated in all those cases in which lithium salts would be given and in which at the same time the tonic action of the glycerophosphates seems called for. First and foremost comes gout, accompanied by nervous symptoms and debility. It is also of benefit in sciatica, rheumatism and calculus. It is given 3—4 times a day in doses of 0.5—4.0 grammes ( $7\frac{1}{2}$ —60 grains) in water, soda water, or aerated lemonade.

### Magnesium Glycerophosphate

has the same uses and dosage as the sodium salt. In chronic constipation it should be given in larger doses (5—10 grammes [75—150 grains] as a dose, daily).

### Manganese Glycerophosphate

may be given alone or in combination with iron glycerophosphate in the same doses and for the same diseases as the last named salt. For preparing solutions soluble manganese gly-

cerophosphate is prescribed, for pills and powders neutral manganese glycerophosphate.

#### Bismuth Glycerophosphate

is given alone or combined with other suitable drugs, such as bismuth subnitrate, in affections of the stomach and intestines, dyspepsia, diarrhoea, vomiting with diarrhoea, cholera, dysentery, ulcer of the stomach or intestine, cardialgia, acidosis, etc., in doses of 0.5—1.0 gramme ( $7\frac{1}{2}$ —15 grains) 3—4 times daily.

#### Strontium Glycerophosphate.

As strontium salts are non-poisonous, and, according to Laborde, improve the appetite and the state of nutrition, strontium glycerophosphate is a drug deserving of special interest in general debility, especially after exhausting diseases, in convalescence, pulmonary tuberculosis, albuminuria, rickets, tænia, etc. 0.5—1.0 gramme ( $7\frac{1}{2}$ —15 grains), are given several times daily, or when necessary (in tænia) up to 10 grammes (150 grains) a day, preferably in the form of powders.

#### Zinc Glycerophosphate.

No special indications have as yet been given for this salt. It might be used in the place of zinc phosphate in the treatment of epilepsy and other nervous complaints, and also as an astringent and antispasmodic. As larger doses might conceivably cause vomiting, as does zinc sulphate, it is best to begin with small single doses of 0.01—0.05 gramme ( $\frac{1}{6}$  to  $\frac{3}{4}$  grain). On no account should a larger dose than 1 gramme (15 grains) daily be given without a previous examination of the individual. Externally the salt might certainly be used like zinc acetate as a caustic, astringent and antiseptic. I have no references to this form of its employment.

#### Quinine Glycerophosphate.

According to Moncourt, quinine glycerophosphate has the advantage over the other quinine salts that it has no noxious by-effects. It does not upset the stomach, nor does it cause buzzing in the ears and it can be taken for a pro-

longed period, as the patient does not become habituated to the drug and its efficacy is thus not diminished. Moncourt assumes that a diminution in the efficacy of the other quinine salts after prolonged use occurs owing to the quinine gradually causing poisoning of the nerve cells. But if the medicament be united to a substance which promotes the new formation of nerve tissue, as is the case with glycerophosphoric acid, the disadvantage mentioned above is eliminated and the beneficial action of the quinine is in no way interfered with, even after prolonged administration. In malaria this circumstance is said to be specially noteworthy.

In fever quinine glycerophosphate is given in doses of 0.5—1.0 gramme ( $7\frac{1}{2}$ —15 grains), as an antineuralgic 0.3 to 0.6 gramme (5—10 grains) are given daily, and as a tonic single doses of 0.1—0.2 gramme ( $1\frac{1}{2}$ —3 grains), and daily doses of 0.2—0.4 gramme (3—6 grains). As a tonic it may be employed in the place of quinine wine. It is prescribed in cachets or as pills.

### Strychnine Glycerophosphate.

This preparation can be prescribed in the same way as strychnine nitrate. But it is specially suitable in cases such as tuberculosis, anæmia, debility, etc., in which the glycerophosphates of calcium, sodium or iron are to be administered in combination with strychnine, as was suggested by Robin. Given by itself it has no advantage over strychnine nitrate, because its maximum dose of 0.01 gramme ( $\frac{1}{6}$  grain) a day contains such a small amount of glycerophosphoric acid that it can have no therapeutic significance. As a substitute for the syrup of glycerophosphates formerly recommended by Robin, the following powder might prove very useful:

Rp. Calcii glycerophosph.	5.0 grammes (75 grains)
Potassii glycerophosph.	2.5 grammes (38 grains)
Sodii glycerophosph.	2.5 grammes (38 grains)
Magnesii glycerophosph.	2.5 grammes (38 grains)
Ferri glycerophosph.	1.25 grammes (20 grains)
Strychnin. glycerophosph.	0.06 gramme (1 grain)
Caffein.	1.25 grammes (20 grains)
Sacchari lactis	ad 100.0 grammes ( $3\frac{1}{3}$ oz)

M. f. p. det. ad vitrum bene clausum.

Sig. A pinch to be taken several times daily during or after meals.

The mixture may also be prescribed in separate powders of 1—3 grammes (15—45 grains). It is scarcely necessary to exceed a single dose of 3 grammes (45 grains) or a daily dose of 9 grammes (135 grains). It may be borne in mind, however, that the maximum single dose of strychnine is contained in 10 grammes (150 grains) and the maximum daily dose in 20 grammes (300 grains) of the powder.

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# Digitalis Glucosides and Allied Drugs.

## 1. General and Historical.

Since the introduction of digitalis leaves into therapeutics by Withering of Birmingham in 1775, digitalis has become an indispensable drug in our materia medica. But in spite of many efforts it has as yet been impossible to isolate from this drug a uniformly active substance, which could fully replace digitalis leaves and supplant them in our list of most important remedies. However, the work of Homolle, Quevenne, Walz, Nativelle, Schmiedeberg and Kiliani has led to the isolation of a number of digitalis glucosides, several of which are much valued in therapeutics.

From the work of the above named authors it is apparent that the digitalis plant contains several glucosides, the physiological action of which varies considerably, both qualitatively and quantitatively. Therefore, before entering upon a consideration of the practical employment of digitalis and of its glucosides, the latter must be examined more closely with regard to their chemical composition and their physiological action. This is imperative for the reason that the nomenclature adopted by different authors in the literature on this subject has led to such confusion as is scarcely met with in any other field of pharmacy or pharmacology.

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Homolle, *Journal de pharmacie et de chimie* 1845, I, p. 57.

Homolle-Quevenne, *Neues Repertorium für Pharmazie* Vol. 9, p. 2.

*Gazette des hôpitaux* 1850, p. 53. *Union médicale* 1851, p. 69.

Walz, *Jahrbuch für praktische Pharmazie* Vol. 14, p. 20; Vol. 21, p. 29, Vol. 24, p. 86.

Nativelle, *Journal de pharmacie et de chimie* 1869, I, p. 255; 1872, II, p. 430; 1874, II, p. 81.

Schmiedeberg, *Archiv für experimentelle Pathologie und Pharmacologie* 1875, p. 16. — *Neues Repertorium der Pharmazie* Vol. 24, p. 89.

Kiliani, *Archiv der Pharmazie* 1892, p. 250; 1896, p. 273, 481; 1897, p. 425; *Berichte der deutschen chemischen Gesellschaft* Berlin 1890, p. 1555; 1891, p. 339 and 3951; 1898, p. 2454; 1899, p. 2196 and 2201.

The first digitalis glucoside to attain any degree of importance in therapeutics was digitalin, prepared by Homolle (1845) from the leaves of *Digitalis purpurea*. Until that time all attempts to isolate an active principle from digitalis had been unsuccessful. Thus Bonjean in 1843, only two years before the publication of Homolle's work, mistook a resinous body for the active substance of digitalis. Homolle himself enumerates the following as his predecessors in the field of research regarding digitalis: Bidault, Planavia, Leroyer, Rein, Haase, Welding, Dulong, Henry, Quevenne, and Tromsdorff. Homolle's method for preparing his digitalin was that formerly much in vogue for the isolation of glucoside-like vegetable substances. This method consisted in clearing the aqueous extract of the drug with subacetate of lead, and after separation from the lead, precipitating with tannic acid; the combination of glucoside and tannin thus formed was decomposed by adding lead oxide, and the glucoside thus set free was then extracted with alcohol. After the evaporation of the alcohol, impure digitalin remained, this was then freed from fat by means of ether, rendered colourless by animal charcoal and then precipitated from alcohol. The preparation thus obtained consisted of both amorphous and crystalline substances, for which reason the digitalin of Homolle has been described in the literature sometimes as an amorphous and sometimes as a crystalline body. The French pharmacopœia of 1866 retained the method of preparing digitalin as described by Homolle; but this yielded a preparation which was not completely soluble in chloroform. For this reason the pharmacopœia in question required that the digitalin should be redissolved in chloroform and the latter evaporated. In this way "digitaline chloroformique" was obtained, a yellowish-brown, amorphous preparation, completely soluble in alcohol and in chloroform.

Digitalin was now further investigated by Homolle in conjunction with Quevenne, and they succeeded in isolating three different substances from digitalin. By treating it with a mixture of alcohol and ether of specific gravity 0.78, these authors obtained an insoluble residue and a solution. The former they named "le digitalin". The sol-

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Bonjean, Journal de pharmacie et de chimie 1843, p. 23.

ution in alcohol and ether, when evaporated, left a residue which was only partially soluble in alcohol (50 p. c.). They named the soluble portion "la digitaline", and the insoluble portion "digitalose".

It may be here mentioned that Homolle's further researches, and the nomenclature adopted by him, already introduced a considerable degree of confusion, for the author unfortunately made a distinction between digitalin and digitaline. I shall therefore in the following remarks always add the name of the author, when necessary, in order to avoid errors.

Two years after Homolle's first publication regarding digitalin, Walz began his reports dealing with his work on this subject. He first prepared an alcoholic extract of digitalis leaves and precipitated those substances which were soluble in water (e. g., its aqueous extract) with tannic acid. When decomposed by lead oxide the tannin compound thus formed constituted the raw digitalin Walz. According to Walz, when this substance is treated with ether, fat and two other substances dissolve; the author named these "digitaloin" and "digitalacrin  $\alpha$  and  $\beta$ ". The residue, which was insoluble in ether, was extracted with water, whereby "digitaletin" remained and "digitalin Walz" dissolved. Walz describes his digitalin as a yellowish, amorphous substance, which is distinguished from the digitalin of Homolle by being soluble in water and only with difficulty soluble in chloroform. The digitalin of Walz formerly also bore the name of "German digitalin", but it should be noted that it is not identical with the digitalinum Germanicum at present on the market, as the latter is prepared from digitalis seeds. However, Walz in the course of his studies on digitalin altered his method of preparation, and later (Cf. Canstatt's Jahresbericht 1850, Vol. 10, p. 22) he describes his digitalin as a crystalline body, very similar to the digitalin of Homolle, soluble with difficulty in water, melting at 175°.

Nativelle isolated three substances from digitalis leaves, namely digitalein Nativelle, a glucoside soluble in water, prepared by extraction with water and subsequent purification, and digitalin Nativelle, (digitaline cristallisée), soluble in alcohol and chloroform, obtained by extraction with alcohol, and thirdly digitin Nativelle,

MERCK'S REPORTS 1911.

soluble in alcohol and practically insoluble in chloroform; this substance, on account of its physiological inactivity, he at first named "substance cristallisée inerte".

Schmiedeberg obtained from digitalis leaves the first preparation of digitalis which had well defined chemical characteristics and was physiologically active, viz., digitoxin Schmiedeberg; he first extracted the drug with water and then with alcohol (50 p.c.), the alcoholic extract was cleared with lead acetate, and after removing the lead which had dissolved, evaporated the solution to dryness, and extracted the residue with chloroform and distilled off the chloroform. After purifying the residue with ether and animal charcoal, as well as recrystallising it several times from alcohol, he obtained a pure hydrated preparation, melting at  $145^{\circ}$  C. For anhydrous digitoxin he gave the empirical formula  $C_{21}H_{32}O_7$ . Digitoxin Schmiedeberg is now simply called "digitoxin". Kiliani, who has made an exhaustive study of digitoxin and its decomposition products, found that this glucoside corresponded to the formula  $C_{34}H_{54}O_{11}$ , and on hydrolysis yielded digitoxigenin and digitoxose. It forms white crystals, which are readily soluble in alcohol and chloroform, but only with difficulty soluble in water and ether.

Kiliani found another glucoside in digitalis leaves. This is a crystalline body, similar to digitoxin, which Kiliani named "digitophyllin". He states that its formula is  $C_{32}H_{52}O_{10}$  and its melting point  $231^{\circ}$  C.

The researches of Schmiedeberg and Kiliani also yielded another body with definite chemical characteristics, viz., digitonin, with the formula  $C_{54}H_{92}O_{28}$ \*) which decomposes at a temperature above  $235^{\circ}$  C. without having a well defined melting point. It is practically insoluble in water, ether and chloroform, it is more readily soluble in alcohol (80—85 p.c.). It is preferable to call this body digitonin Kiliani, because digitonin Schmiedeberg, according to Kiliani, did not represent a pure, uniform substance. Schmiedeberg described his digitonin as an amorphous substance readily soluble in water. Kiliani succeeded in demonstrating that digitonin could be obtained in either an

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\*) See Berichte der deutschen chemischen Gesellschaft Berlin Vol. 32, p. 339 and Vol. 42, p. 239. Note 6.

amorphous or a crystalline form, according to the concentration of the alcohol used in the process of recrystallisation. On examination the amorphous preparation was found to be readily soluble in water, while the crystalline body dissolved with difficulty. Kraft considers the digitonins described by Schmiedeberg and Kiliani to be distinct substances and would like to see the name digitsaponin introduced for digitonin Schmiedeberg. While Kiliani formerly (Archiv der Pharmazie 1892, p. 250) assumed that digitonin was present in both the leaves and the seeds of digitalis, it is stated in his later communications (Archiv der Pharm. 1895, p. 311) that it is only found in the seeds. Kraft states that a body is present in the leaves which can be distinguished from digitonin by its melting point ( $260-265^{\circ}\text{C.}$ ), its solubility and its behaviour towards cholesterin. Digitonin was isolated by Schmiedeberg and Kiliani from digitalinum Germanicum. According to Kiliani, when heated with dilute hydrochloric acid it splits up into digitogenin, dextrose and galactose. (Berichte der deutschen chemischen Gesellschaft Berlin 1891, p. 341).

Schmiedeberg also obtained from digitalin. Germanicum an amorphous digitalin with the formula  $(\text{C}_5\text{H}_8\text{O}_2)_n$ , the chemical individuality of which, in spite of its amorphous constitution, was confirmed by Kiliani. Digitalin Schmiedeberg forms a white mass, readily soluble in alcohol, hot dilute acetic acid and a mixture of alcohol and chloroform, but is only slightly soluble in cold water, chloroform and ether. When split up by acids it forms digitaliresin and glucose. On preparing his digitalin, Schmiedeberg found another glucoside soluble in water, digitalein Schmiedeberg; when treated with acids it is decomposed into glucose and a body probably identical with digitaliresin.

Digitalin Schmiedeberg and digitalein Schmiedeberg were examined more minutely by Kiliani. He was able to prove that pure digitalin, for the preparation of which he worked out an exact formula\*), forms an amorphous white powder, which swells up in water at ordinary temperature and is soluble 1 in 1000 of water. Moreover, it is said to dissolve in

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Kraft, Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 175 and 237.

\*) Archiv der Pharmazie 1892, Vol. 230, p. 252 and 1895, Vol. 233, p. 299.

50 parts of alcohol (50 p. c.) and more readily in hot alcohol. On heating it remains white up to 200° C., begins to sinter at 210° C. and melts at about 217° C. Kiliani gave it the formula  $(C_5 H_8 O_2)_7 = C_{35} H_{56} O_{14}$ , but also mentions that it may have the formula  $C_{36} H_{58} O_{14}$ . According to Kiliani, on heating with dilute alcoholic hydrochloric acid it splits up into digitaligenin, glucose and digitalose. (Archiv der Pharmazie 1892, p. 250.)

Kiliani at first doubted the chemical individuality of the digitalein of Schmiedeberg. Keller and Houdas also took it to be digitonin. But Kiliani proved later that the seeds and leaves of digitalis contain a cardiac poison, soluble in water, which contains no digitalin, the physiological activity of which, therefore, precludes its identity with digitonin. Kiliani and Windaus suspected the presence of a lactone in digitalein, because its neutral aqueous solution gives an acid reaction on standing. This proves digitalein to be a distinct substance, of uniform composition. Kraft, on the other hand, accepts the nomenclature of digitalein only as a generic term for all the active glucosides which are soluble in water and are present in digitalis. He also places in this class gitalin, an amorphous glucoside, melting at 150—155° C., which he isolated from digitalis leaves. It is more readily soluble in cold (1:600) than in hot water. For this reason it is partially precipitated on heating the solution, and at the same time the glucoside is decomposed. In chloroform it is soluble without alteration in all proportions. If gitalin is dissolved at ordinary temperature in 1.5 parts of alcohol and 0.75 parts of water are added, on shaking the mixture gitalin hydrate will separate. This melts at 75° C., and is only slightly soluble in alcohol and water (1:3000). On evaporating the alcoholic solution of gitalin, anhydrogitalin is formed; it appears at first chiefly as an amorphous body, but on recrystallisation from alcohol it can be obtained in crystals melting at 255° C. Gitalin, and also anhydrogitalin, give a permanent violet colour with Kiliani's reagent, similar to digitalinum verum. With Keller's "layering" test

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Keller, Berichte der chemischen Gesellschaft Berlin 1897, p. 125.

Houdas, Comptes rendus 1891, p. 648.

Kiliani-Windaus, Archiv der Pharmazie 1899, p. 458.

Kraft, Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 162 and 173.

gitalin gives an indigo colour with the glacial acetic acid and a violet ring at the juncture of the glacial acetic acid and the sulphuric acid.

Digitalinum Germanicum\*), obtained from digitalis seeds, is essentially a mixture of digitalin Schmiedeberg, digitonin and digitalein. It dissolves in water and alcohol, but is practically insoluble in chloroform. (Kiliani, Archiv der Pharmazie, 1895, 299.)

In order to obtain a clearer view of the subject, those substances of digitalis with which we have already become acquainted, their synonyms and their derivatives are enumerated\*\*) in the following remarks and briefly dealt with on the basis of the considerations mentioned above or contained in the literature:

Acrodigitalins are, according to Ludwig, those digitalis substances which do not possess the characteristics of glucosides. (Archiv der Pharmazie, Vol. 194, p. 213.)

Anhydrodigitoxigenin is obtained by the action of concentrated hydrochloric acid on digitoxigenin in alcoholic solution. It crystallises in colourless prisms corresponding to the formula  $C_{22}H_{30}O_3$ . (Kiliani, Berichte der deutschen chemischen Gesellschaft, Berlin 1898, p. 2458.)

Anhydrodigitic acid,  $C_{10}H_{14}O_3$ , occurs in two isomeric modifications,  $\alpha$ -acid and  $\beta$ -acid. The  $\alpha$ -acid is formed from digitic acid by the action of dehydrating agents. It loses its water of crystallisation at  $140^\circ C$ . and melts at  $170^\circ C$ . The  $\beta$ -acid melts at  $263^\circ C$ . (Kiliani, Archiv der Pharmazie 1894, p. 334.)

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\*) According to J. Pereira (Handbuch der Heilmittellehre, translated by R. Buchheim Vol. 2, p. 293), the seeds of Digitalis purpurea were used medicinally in England, as well as digitalis leaves, in the first half of the 19<sup>th</sup> century, as they were considered more constant in their action than the leaves. The first examination of the seeds for digitalin was undertaken by A. Buchner (Buchners Repertorium für Pharmazie 1851, Vol. 9, p. 38. — Canstatt's Jahresberichte 1851, N. F. 1. Jahrgang p. 44.)

\*\*) In the following description a few special preparations containing digitalis substances are mentioned, as their names resemble the word digitalis.

Anhydrogitaligenin, according to Kraft, is formed during the hydrolysis of anhydrogitalin, together with digitoxose and a non-crystalline sugar. It crystallises from alcohol, melts at  $119^{\circ}\text{C.}$ , and gives a deep violet coloration with Kiliani's reagent. (Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 173.)

Anhydrogitalin is a product of decomposition of gitalin *q. v.*

Desoxydigitogenic acid,  $\text{C}_{28}\text{H}_{42}\text{O}_9$ , is obtained by the reduction of digitogenic acid by means of sodium amalgam. (Kiliani, Archiv der Pharmazie 1893, p. 448. Berichte der deutschen chemischen Gesellschaft Berlin 1899, p. 2201.)

Digalen, see digitoxin soluble Cloetta.

Digitalacrin ( $\alpha$ - and  $\beta$ -) are components of raw digitalin Walz (cf. page 33).

Digitalein Nativelle was described by Nativelle as a physiologically active glucoside, soluble in water and obtained from digitalis leaves. (Moniteur scientifique 1874, p. 822. — Houdas, Comptes rendus de l'académie des sciences, Vol. 113, p. 648.)

Digitalein Schmiedeberg is a glucoside soluble in water. For details see page 35. (Archiv für experimentelle Pathologie 1875, Vol. 3, p. 33. — Houdas, Comptes rendus de l'académie des sciences, Vol. 113, p. 648. — Kiliani, Berichte der deutschen chemischen Gesellschaft Berlin 1891, p. 3950, and Archiv der Pharmazie 1899, p. 458. Keller, Berichte der deutschen pharmazeutischen Gesellschaft 1897, p. 125.)

Digitaléine Buignet represented the glucosides of digitalis leaves which were soluble in water. (Journal de pharmacie et de chimie 1872, I, p. 191.)

Digitalen is a special preparation for therapeutic use, viz., a solution of digitalis glucosides containing glycerin. (Lüders, Chemische Industrie 1905, p. 261.)

Digitaletin is a product of decomposition of digitalin Walz and is formed from the latter together with sugar

by the action of hydrochloric acid. (Compare Roscoe and Schorlemmer, *Lehrbuch der organischen Chemie* 1901, part 6, p. 682.) The portion of raw digitalin Walz insoluble in ether and water was also included under the name of digitaletin. (Conf. p. 33.)

Digitalicrin, according to Wiggers (*Canstatt's Annual Reports* 1850, Vol. 10, p. 23), is a constituent of digitalin Walz (raw digitalin), a substance with an acrid and harsh taste, of the formula  $C_{11}H_{20}O_3$ .

Digitalid, digitalidine and digitalosin are substances which Homolle, in his later publications, states that he found in the leaves of digitalis besides his digitalin. (Roscoe and Schorlemmer, *Lehrbuch der organischen Chemie* 1901, part 6, p. 682.)

Digitaligenin is a crystalline body corresponding to the formula  $C_{22}H_{30}O_3$ , melting at about  $211^{\circ}C.$ , and formed in the decomposition of digitalin Kiliani. This preparation is soluble in alcohol and insoluble in water, and is said to have no physiological action. (Kiliani, *Archiv der Pharmazie* 1892, p. 250. *Berichte der deutschen chemischen Gesellschaft* Berlin 1898, p. 2454.)

Digitalin with no other specification is a vague term, and should be avoided in the literature and in practice in order to eliminate a source of errors and of confusion. The same applies to digitalinum and digitaline.

Digitalin, amorphous. This designation is probably chiefly intended to cover digitalinum Gallicum (digitaline chloroformique) of the French pharmacopœias of 1866 and 1895, a substance which is completely soluble in chloroform. But it must be remembered that digitalinum verum and digitalinum Germanicum are also amorphous.

Digitalin(um) crystallisatum has so far been used as a synonymous term for digitonin. As this is misleading it would be better to avoid its use altogether. In commerce, however, names which have once been introduced are difficult to get rid of. Kiliani objected to the term "digitalin cryst." as early as 1891. (*Berichte der deutschen chemischen Gesellschaft* Berlin 1891, p. 3953.)

Digitalin Henry was a mixture of glucosides from digitalis leaves. (Journal de pharmacie et de chimie 1845, I, p. 460.)

Digitalin Homolle is a mixture of glucosides and their products of decomposition contained in digitalis leaves, and is practically insoluble in water. (Conf. p. 32.)

Digitalin Homolle-Quevenne is the constituent of digitalin Homolle which is insoluble in a mixture of alcohol and ether. (Compare above.)

Digitalin Kiliani is identical with digitalinum verum, *q. v.*

Digitalin Lancelot was a mixture of amorphous digitalis glucosides, which was prepared from digitalis leaves according to the directions given by Lancelot. (Die Pflanzenstoffe von Husemann und Hilger, 2<sup>nd</sup> edition, p. 1234.)

Digitalin Lebourdais was a crystalline preparation obtained from digitalis leaves. (Annales de chimie et de physique, 3<sup>rd</sup> series, Vol. 24, p. 58.)

Digitalin Nativelle is a crystalline product prepared from digitalis leaves, which is probably not unlike digitoxin in constitution. According to Schmiedeberg and Kiliani, it is a mixture of several substances. (Berichte der deutschen chemischen Gesellschaft 1891, p. 3951, 1898, p. 2462.) Compare also p. 33 and Berichte der deutschen chemischen Gesellschaft Berlin 1898, p. 2454. — Journal de pharmacie et de chimie 1874, II, p. 81.

Digitalin Schmiedeberg is a chemically uniform, amorphous body of the formula  $(C_5 H_8 O_2)_7$ . (Archiv für experimentelle Pathologie 1875, p. 16.)

Digitalin Walz was a mixture of glucosides from digitalis leaves (compare above). (Delffs, Neues Jahrbuch für Pharmazie 1858, p. 25 [Vol. 9]. — Wittstein, Wittsteins Vierteljahresschriften für praktische Pharmazie 1865, Vol. 14, p. 76.)

“La digitaline” is digitalin Homolle or Homolle-Quevenne.

Digitaline amorphe chloroformique is digitalinum Gallicum amorph.

Digitaline amorphe française is digitalinum Gallicum amorph.

Digitaline chloroformique is digitalinum Gallicum amorph.

Digitaline pharmacopée française 1884 is digitalinum Gallicum amorph.

Digitaline cristallisée is either digitalin Nativelle or digitoxin. Formerly it also applied to digitonin.

Digitaline cristallisée Pharmacopée française 1908 is identical with digitoxine Pharmacopée franç. 1908. (Conf. Digitoxine Pharm. franç.)

Digitaline cristallisée française is digitalin Nativelle.

Digitaline française is digitalinum Gallicum amorph.

Digitaline Homolle-Quevenne is the constituent of digitalin Homolle which is soluble in a mixture of alcohol and ether and in dilute alcohol, but is not identical with digitalin Homolle-Quevenne, which is insoluble in a mixture of alcohol and ether.

Digitaline Kosmann was a crystalline preparation which Kosmann extracted from the lead precipitate obtained in the preparation of digitalin Homolle. (Journal de connaissance médicale pratique 1845, Vol. 13, p. 67.)

Digitaline passive was the name which Nativelle at first gave to his digitin.

Digitaline Pharmacopée Belge II. is digitalinum Gallicum amorph.

Digitalinic acid (acide digitalinique) was the name given by Kosmann to a body corresponding to the formula  $C_{22}H_{35}O_{12}$ , and obtained by heating digitalin Kosmann with caustic soda. (Journal de pharmacie et de chimie 1860, II, 15. Homolle, Union médicale 1872, p. 80.)

Digitalic acid Morin is a substance obtained from digitalis leaves. Morin prepared a volatile acid by submitting digitalis leaves to steam distillation and called it "antirrhinic acid" (most probably identical with valerianic acid). He describes it as a colourless, oily mass, soluble in alcohol, but insoluble in water; it dissolves very grad-

ually in water, with which it forms a hydrate. It possesses a characteristic smell and taste. (*Journal de pharmacie et de chimie* 1845, I, p. 294.)

*Digitalinum fluidum* was the name given by Engelhardt to a liquid, volatile, oily substance obtained from digitalis leaves, and which he regarded as the active component of digitalis. (*Zeitschrift für Chemie und Pharmazie* 1862, p. 722.)

*Digitalinum Pharmacopée française* 1908 is identical with digitoxine *Pharm. franç., q. v.*

*Digitalinum Gallicum amorph.* is obtained from digitalis leaves according to the method given in the *Pharmacopée française* 1884. It also bears the name of "digitaline chloroformique". It is completely soluble in chloroform and practically insoluble in water. (*Conf.* p. 32.)

*Digitalinum Gallicum crystallisatum* is either digitalin *Nativelle* or digitoxine *pharm. franç.* 1908.

*Digitalinum Germanicum* is an amorphous product obtained from digitalis seeds, and is soluble in water. It consists principally of digitalinum verum, digitalein and digitonin. It was examined in detail by Schmiedeberg and Kiliani. (*Archiv für experimentelle Pathologie* 1875, p. 16. — *Berichte der deutschen chemischen Gesellschaft* 1890, p. 1555.)

*Digitalinum passivum* was the name given by *Nativelle* to digitin.

*Digitalinum verum* is digitalin *Schmiedeberg* of the formula  $C_{35}H_{56}O_{14}$ . (*Archiv für Pharmazie* 1892, p. 250, 1895, p. 299 and 698, 1899, p. 455 and 458. *Berichte der deutschen chemischen Gesellschaft Berlin* 1898, p. 2455.)

*Digitaliresin* is a body formed from digitalin *Schmiedeberg* by hydrolysis. (*Chemisches Zentralblatt* 1875, p. 262. *Archiv für experimentelle Pathologie*, Vol. 3, p. 30 and Vol. 4, p. 191.)

*Digitaliretin*,  $C_{30}H_{25}O_{10}$ , is, according to *Kosmann*, an amorphous body formed by the splitting up of digitalin *Kosmann* under the action of sulphuric acid; it is only slightly soluble in water, alcohol and ether, but dissolves in hot alcohol. (*Journal de pharmacie et de chi-*

mie 1860, II, p. 1. — Rochleder, *Chemisches Zentralblatt* 1863, p. 46. — Schmiedeberg, *Archiv für experimentelle Pathologie*, Vol. 3, p. 26.) Walz also obtained a digitaliretin by the decomposition of his digitaletin q. v. Neither the preparation of Kosmann nor that of Walz can lay claim to uniformity. (Husemann-Hilger, *Pflanzenstoffe*, 2<sup>nd</sup> edition p. 1235.)

Digitaloin is a component of raw digitalin Walz. (Conf. p. 33.)

Digitalon is the lactone of digitalonic acid. Melting point 138—139°C. The name "digitalon" is also given to a special preparation — a solution of all the glucosides present in digitalis — to be used subcutaneously in doses of 0.5 to 1 c.c. (*Pharmazeutische Zeitung* 1904, p. 760, *Therapie der Gegenwart* 1905, p. 398.)

Digitalonic acid,  $C_7H_{14}O_6$ , is obtained by the oxidation of digitalose. (*Berichte der deutschen chemischen Gesellschaft*, Berlin 1892, p. 2116, 1898, p. 2454, 1905, p. 3621, 1909, p. 2610.)

Digitalose is a sugar corresponding to the formula  $C_7H_{14}O_5$ , formed together with digitaligenin and grape sugar by the hydrolysis of digitalin Kiliani. (Kiliani, *Archiv der Pharmazie* 1892, p. 250, 1898, p. 2460.)

Digitalosé Homolle-Quevenne is the component of digitalin Homolle which is soluble in a mixture of alcohol and ether, and insoluble in dilute alcohol. (Compare page 33.)

Digitalosmin was the name given by Walz to the odorous principle of *Digitalis purpurea*; he obtained it by steam distillation from the herb in the form of yellowish-white scales, which glisten like mother-of-pearl, soluble in alcohol or ether and in hot water. They bore a strong smell characteristic of dry digitalis leaves. (*Jahrbuch für praktische Pharmazie* 1852, Vol. 24, p. 86.)

Digitasolin was the name at first given by Walz to his digitalin (compare Roscoe and Schorlemmer, *Lehrbuch* 1901, VI, p. 682). According to Wiggers, however, it is a constituent of (raw) digitalin Walz, which Walz subsequently divided into (what he called) true, pure

digitalin, digitalicrin and digitalosin. He gave the melting point of his pure digitalin as  $175^{\circ}\text{C}$ ., and the melting point of digitalosin as  $137.5^{\circ}\text{C}$ . (Compare Wiggers, *Canstatts Jahresberichte* 1850, Vol. 10, p. 23.)

**Digitin Nativelle** was described by Nativelle as a crystalline substance, insoluble in water, which possessed neither taste nor physiological action. It was prepared by the author from *digitalis* leaves and cannot therefore be identified with digitonin. (*Moniteur scientifique* 1874, p. 822.)

**Digitoflavone** is a yellow pigment present in *digitalis* leaves; it forms crystals and is identical with luteolin. (Fleischer, *Dissertation Freiburg* 1898. *Berichte der deutschen chemischen Gesellschaft Berlin* 1899, p. 1184 and 1901, p. 1453.)

**Digitogenin** is a substance which has the formula  $\text{C}_{30}\text{H}_{48}\text{O}_6$ , or  $\text{C}_{30}\text{H}_{50}\text{O}_6$ , formed by hydrolysis from digitonin; it crystallises in fine needles and melts at a temperature above  $250^{\circ}\text{C}$ . Compare page 35. (*Archiv der Pharmazie* 1892, p. 261 and 1893, p. 448. — *Berichte der deutschen chemischen Gesellschaft Berlin* 1890, p. 1555, 1891, p. 339 and 3951, 1899, p. 2201, 1901, p. 3562. — *Archiv für experimentelle Pathologie*, Vol. 3, p. 24.)

**Digitogenic acid**, according to Kiliani, is an  $\alpha$ -ketonic acid, and is formed by the oxidation of digitogenin by means of chromic acid. It is a dibasic acid of the formula  $\text{C}_{28}\text{H}_{44}\text{O}_8$ . (*Berichte der deutschen chemischen Gesellschaft Berlin* 1891, p. 343 and 1899, p. 2203. — *Archiv der Pharmazie* 1893, p. 448 and 1899, p. 466.)

$\beta$ -**Digitogenic acid**,  $\text{C}_{28}\text{H}_{44}\text{O}_8$ , is formed by heating digitogenic acid to  $160^{\circ}\text{C}$ . Colourless crystals melting at  $105^{\circ}\text{C}$ . (Kiliani, *Archiv der Pharmazie* 1899, p. 466. — *Berichte der deutschen chemischen Gesellschaft Berlin* 1899, p. 2205.)

**Digitoleinic acid**. Kosmann precipitated an aqueous extract of *digitalis* leaves with lead subacetate and treated the precipitate thus produced by warming with a solution of sodium carbonate. By treating the liquid with sulphuric acid, he was able to precipitate two substances; of these the one soluble in ether was called by him *dig-*

toleinic acid. It forms a fatty, granular mass. (Journal de connaissance médicale 1845, Vol. 13, Buchners Repertorium für Pharmazie 1846, Vol. 92, p. 348.)

Digitonein, according to Schmiedeberg, is a body formed by the decomposition of digitonin by means of hydrochloric acid; it is insoluble in ether. (Archiv für experimentelle Pathologie, Vol. 3, p. 22.)

Digitonin, when anhydrous, occurs as an amorphous body, while with  $5\text{H}_2\text{O}$  it is a crystalline, chemically uniform body; its formula is  $\text{C}_{54}\text{H}_{92}\text{O}_{28}$  or  $\text{C}_{54}\text{H}_{92}\text{O}_{28} + 5\text{H}_2\text{O}$ . (Compare page 35.)

Digitonin, amorphous, is digitonin Schmiedeberg.

Digitonin cryst. is digitonin Kiliani.

Digitonin Kiliani is pure, crystalline, hydrated digitonin ( $\text{C}_{54}\text{H}_{92}\text{O}_{28} + 5\text{H}_2\text{O}$ ). (Archiv der Pharmazie 1893, p. 460. — Berichte der deutschen chemischen Gesellschaft Berlin 1891, p. 339 and 3951.)

Digitonin Schmiedeberg is amorphous, anhydrous digitonin ( $\text{C}_{54}\text{H}_{92}\text{O}_{28}$ ). According to Kraft, digitonin Schmiedeberg and digitonin Kiliani are not identical; he therefore suggests the designation "digitsaponin" for digitonin Schmiedeberg. (Kraft, Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 175.)

Digitophyllin, according to Kiliani, is a chemically uniform body with the formula  $\text{C}_{32}\text{H}_{52}\text{O}_{10}$ . According to Keller, Arnaud and Adrian, it is identical with the French digitaline cristallisée. But neither the identity nor the dissimilarity of these two digitalis products has as yet been conclusively proved. (Archiv der Pharmazie 1897, Vol. 235, p. 426. — van Rijn, The glucosides 1900, p. 425.)

Digitoresin, according to Schmiedeberg, is a substance soluble in ether, formed by treating digitonin with hydrochloric acid. (Compare above.) (Archiv für experimentelle Pathologie, Vol. 3, p. 22.)

Digitonic acid,  $\text{C}_{26}\text{H}_{12}\text{O}_7$ , melts at  $210^\circ\text{C}$ . It is formed, together with  $\beta$ -digitogenic acid, on heating digitogenic acid to  $160^\circ\text{C}$ ., or by warming it with solution of caustic potash. (Edinger, Berichte der deutschen chemischen Ge-

sellschaft Berlin 1899, p. 339. — Kiliani, Archiv der Pharmacie 1899, p. 466. — Berichte der deutschen chemischen Gesellschaft Berlin 1899, p. 2201.)

Digitoxigenin,  $C_{22}H_{32}O_4$ , is a product of decomposition of digitoxin. It is formed, together with a sugar, so-called digitoxose, by the treatment of digitoxin with alcoholic hydrochloric acid at ordinary temperature. Digitoxigenin crystallises in colourless crystals, melting at about  $230^{\circ}C$ . (Archiv der Pharmazie 1895, p. 311 and 1896, p. 481. — Berichte der deutschen chemischen Gesellschaft Berlin 1899, p. 2197.)

Digitoxin (solubile) Cloetta, according to Cloetta, is an amorphous modification of digitoxin, and is only distinguished from the latter by the smaller size of its molecule and its greater solubility in water. Kiliani, however, is of the opinion that digitoxin Cloetta (digalen) is identical with digitalein. (Cloetta, Münchener medizinische Wochenschrift 1904, p. 1466 and 1906, p. 2281. — Kiliani, *ibid.* 1907, p. 886. — Chemisches Zentralblatt 1907, II, 83. — Merck's Report 1907, p. 88.)

Digitoxin, according to Schmiedeberg and Kiliani, is a chemically uniform substance, which is present in the leaves but not in the seeds of digitalis. Kiliani gave it the formula  $C_{34}H_{54}O_{11}$ . (Compare above.)

Digitoxin Kiliani	} are identical with digitoxin.
Digitoxin Schmiedeberg	

$\beta$ -Digitoxin is digitoxin Kiliani	} both are identical.
$\alpha$ -Digitoxin is digitoxin Schmiedeberg	

(Archiv der Pharmazie 1895, p. 311 and 1896, p. 277 and 481.)

Digitoxine Pharmacopée française is essentially identical with digitoxin. The French pharmacopœia requires, *inter alia*, that the preparation shall give a green colour when dissolved in concentrated sulphuric acid, whereas commercial digitoxin gives a brown colour on solution. It also requires incorrectly that the preparation shall not dissolve in benzol (benzene). As a matter of fact, however, digitoxin is soluble in benzol ( $C_6H_6$ ) and not in petroleum benzin (aether petrolei). The error

of the French pharmacopœia, therefore, is due to the faulty or misleading translation of the German "Benzin" into "benzine", which in French is equivalent to benzol.

**Digitoxinic acid**,  $C_{34}H_{56}O_{12}$ , occurs in the form of the sodium salt on heating digitoxin with alcoholic caustic soda. (Kiliani, *Archiv der Pharmazie* 1899, p. 466. — *Berichte der deutschen chemischen Gesellschaft Berlin* 1899, p. 2200.)

**Digitoxonic acid**,  $C_6H_{12}O_5$ , is obtained by the oxidation of digitoxose. (*Berichte der deutschen chemischen Gesellschaft Berlin* 1905, p. 4040, 1908, p. 656 and 1909, p. 2610.)

**Digitoxose**,  $C_6H_{12}O_4$ , is the sugar formed together with digitoxigenin in the hydrolysis of digitoxin. White crystals melting at  $101^{\circ}C$ . (Kiliani, *Archiv der Pharmazie* 1895, p. 311 and 1896, p. 486. — *Berichte der deutschen chemischen Gesellschaft Berlin* 1898, p. 2455; 1899, p. 2196; 1905, p. 4040.)

**Digitsaponin** is a designation suggested by Kraft for digitonin Schmiedeberg. (*Schweizer Wochenschrift für Chemie und Pharmazie*. 1911, p. 175.)

**Digitic acid** is obtained from digitogenic acid by oxidation with potassium permanganate. It crystallises in needles melting at  $192^{\circ}C$ ., and, according to Kiliani, it has the formula  $C_{20}H_{32}O_8$ . (Kiliani, *Berichte der deutschen chemischen Gesellschaft Berlin* 1891, p. 346, and 1899, p. 339. — *Archiv der Pharmazie* 1893, p. 448.)

**Digic acid**,  $C_{16}H_{24}O_6$ , is an amorphous acid, which can be obtained by oxidation of the mother-lye of digitic acid. (Kiliani, *Archiv der Pharmazie* 1894, p. 334.)

**Dixgeninic acid**,  $C_{22}H_{34}O_5$ , is obtained in the form of needle shaped crystals melting at  $225^{\circ}C$ . by heating digitoxigenin with alcoholic solution of caustic soda. (Kiliani, *Berichte der deutschen chemischen Gesellschaft Berlin* 1899, p. 2198.)

**Gitalin** is a glucoside which was obtained by Kraft from digitalis leaves (compare p. 36); it is soluble in 600 parts of cold water. According to Schmiedeberg, it corresponds in strength of its physiological action to digi-

talinum verum. (Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 163.)

Gitalin hydrate is, according to Kraft, obtained from gitalin by dissolving the latter in  $1\frac{1}{2}$  parts of alcohol at ordinary temperature and adding  $\frac{3}{4}$  of a part of water. It separates in crystals. (Compare also gitalin p. 36.) (Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 162.)

Glucodigitalins was the name given by Ludwig to those preparations of digitalis, which were proved to have the characteristics of glucosides, in contradistinction to acrodigitalins (which see). Archiv der Pharmazie, Vol. 194, p. 213.

Hydrodigitonic acid,  $C_{26}H_{44}O_6$ , is formed together with digitonic acid by heating digitogenic acid with solution of caustic potash. It softens at  $240^{\circ}C$ . (Archiv der Pharmazie 1893, p. 457. — Berichte der deutschen chemischen Gesellschaft Berlin 1899, p. 339.)

Oxydigitogenic acid,  $C_{28}H_{42}O_9$ , is obtained from digitogenin by oxidation with potassium permanganate in alkaline solution. (Kiliani, Berichte der deutschen chemischen Gesellschaft Berlin 1891, p. 345, and 1899, p. 2205.)

Paradigitogenin is formed under special conditions during the hydrolysis of digitonin. (Archiv für experimentelle Pathologie 1875, Vol. 3, p. 25.)

Pseudodigitoxin is the name given by Burmann to a soluble glucoside, similar to gitalin, and obtained from digitalis leaves. (Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 33.)

Substance cristallisée inerte (Nativelle) is identical with digitin Nativelle.

Toxigenon,  $C_{20}H_{26}O_3$  or  $C_{19}H_{24}O_3$ , is a crystalline body, formed by the oxidation of digitaligenin or of anhydrodigitoxigenin by means of chromic acid; it commences to decompose at  $220^{\circ}C$ ., without melting. (Kiliani, Berichte der deutschen chemischen Gesellschaft Berlin 1898, p. 2459; 1899, p. 2199.)

Toxiresin is, according to Schmiedeberg, a product of decomposition of digitoxin, soluble in ether. (Archiv für

experimentelle Pathologie 1875, Vol. 3, p. 39, and Vol. 4, p. 191.)

Various colour reactions have been suggested for the chemical identification of the digitalis glucosides; some of these have gained full recognition in laboratory work, but most of them cannot be considered conclusive without the aid of biological tests. The first fairly characteristic reaction was already discovered by Homolle. He found that his digitalin gave an intense green coloration with concentrated hydrochloric acid. To which constituent of digitalin Homolle this coloration is due is uncertain; it may, however, be pointed out that among the digitalis glucosides which have since been studied in detail the only one which gives this reaction is digitoxin. Digitalinum verum is coloured yellow by hydrochloric acid, digitonin remains colourless and on heating with this acid it becomes red.

Later on Homolle's reaction underwent several modifications, some of which were quite unnecessary, with the intention of rendering it more characteristic. Thus Jorissen used a solution of 1 gramme of zinc chloride in 30 grammes of water and 30 grammes of hydrochloric acid. As might have been expected, it gave a green colour with digitalin\*). The second part of Jorissen's reaction, namely that digitalin when evaporated with the zinc chloride solution mentioned above assumes a brown or black colour, cannot be considered characteristic for digitalin, even though Czumpelitz attributes the chestnut-brown colour obtained on evaporating to dryness to be due to the condensing action of the zinc chloride. O. Pape varied Homolle's reaction by mixing digitalin\*) with ten times the amount of starch, adding sufficient concentrated sulphuric acid to form a thick paste and then diluting with hydrochloric or nitric acid. The starch is said to be coloured green by this method. Lafon heated digitalin\*) with a mixture of

Homolle, Union médicale 1872, p. 295.

Jorissen, Chemisches Zentralblatt 1880, p. 376.

\*) This must be a French digitalin, such as digitalin Homolle, digitalin Nativelle, or digitalin amorph. Gallicum, for digitalinum verum never gives a green coloration.

Czumpelitz, Pharmazeutische Post 1881, p. 47.

Pape, Archiv der Pharmazie 1876, p. 233.

Lafon, Comptes rendus de l'académie des sciences Vol. 100, p. 1463.

— Bulletin de la société chimique. Vol. 44, p. 18.

alcohol and sulphuric acid (1:1) until it became yellow and then added a drop of very dilute iron chloride solution. This also gave a green colour. This colour is probably produced by all mineral acids under suitable conditions, and also by sulphuric acid, provided it is not masked by secondary reactions giving dark coloured or black products, or by the brown coloration resulting from its mixture with the red digitalin reaction described below. Flückiger modified the test as follows: he concentrated phosphoric acid (25 p. c.) by heating on a watch glass, and added digitalin Nativelle to the warm acid. The digitalin was coloured green and the acid yellow. The mechanism of the green coloration has not yet been explained.

While digitoxin produces a green coloration with concentrated hydrochloric acid, it causes a greenish-brown to brown colour with concentrated, pure sulphuric acid. Digitalinum verum, on the other hand, is only coloured yellow by sulphuric acid. But if the sulphuric acid contains oxidising substances, such as iron oxide or nitric acid, it yields a deep red colour with digitalinum verum. For this reason Grandeau also used bromine with the sulphuric acid for the digitalin reaction, by exposing the solution of digitalin in sulphuric acid to the action of bromine vapour. In carrying out this reaction a violet-red colour is obtained. Buckingham used a solution of molybdic acid in sulphuric acid, which yields a crimson colour with digitalin. Kiliani describes a digitalin reaction similar to Grandeau's which is probably characteristic of digitalinum verum. If a little digitalin. verum is dissolved in sulphuric acid and a drop of very dilute nitric acid, iron chloride solution, or bromine is added, a bluish-red colour is produced, similar to the colour of digitalis flowers, which soon disappears. The touch of blue in the red coloration has always been considered of special value.

Keller gives the following reactions for the digitalis glucosides. The glucoside is dissolved in 4 c. c. of glacial

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Flückiger, Neues Jahrbuch der Pharmazie Vol. 39, p. 129.

Grandeau, Comptes rendus de l'académie des sciences 1864, Vol. 58, p. 1120.

Buckingham, American Journal of Pharmacy 1873, p. 149.

Kiliani, Archiv der Pharmazie, Vol. 230, p. 250.

Keller, Berichte der pharmazeutischen Gesellschaft Berlin 1895, p. 275.

acetic acid, one drop of a dilute solution of iron chloride is added and the mixture is layered on to 4 c.c. of sulphuric acid. A coloured ring appears at the junction of the liquids. Digitonin gives a pale pink colour, which soon disappears. Digitalin. (verum) gives rise to a carmine ring, still plainly visible as a permanent violet-red colour if only 0.05 milligramme of digitalin is present in 1 c.c. of glacial acetic acid. Digitalein gives a similar coloration, but it is rather fainter and not so constant. Digitoxin at first gives a dirty greenish-brown colour, but very soon the uppermost layer of the sulphuric acid is seen to become brownish-red, while above it a broad, deep bluish-green band is formed, the colour of which soon passes into a permanent indigo-blue. While the mechanism of the green colour reaction of digitoxin cannot be explained, the blue coloration is probably due to the splitting up of the digitoxin, by which digitoxose is formed. This latter most probably causes the blue ring, for Kiliani has found that digitoxose yields a blue colour when dissolved in acetic acid containing iron oxide and sulphuric acid.

In analytical practice, the following reactions for the three most important digitalis glucosides have been extensively adopted, being founded on the observations detailed above:

Digitalin. verum (and digitalin. Germanicum) dissolves in pure concentrated hydrochloric acid, or sulphuric acid, giving a yellow colour. If a drop of dilute ferric chloride solution is added to the solution in sulphuric acid, a red colour containing a touch of blue is immediately produced; the depth of the red coloration varies according to the amount of digitalin present, and it remains constant for days. This coloration is most probably due to digitaligenin, a product of decomposition of digitalin. If sulphuric acid containing iron oxide is used for this reaction, a yellow coloration often appears at first, which lasts for a short time and very soon changes to red. Digitonin is not altered by a similar test; digitoxin is coloured a dirty greenish-brown or brown.

Digitoxin is most easily recognised by Keller's reaction described above; it may also be carried out in the

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Kiliani, Berichte der deutschen chemischen Gesellschaft Berlin 1898, p. 2454.

following modification. To 100 c.c. of concentrated sulphuric acid about 1 c.c. of a 5 p.c. aqueous solution of ferric sulphate is added, while a mixture of 1 c.c. of the same ferric sulphate solution with 100 c.c. of glacial acetic acid is also prepared. If now a trace of digitoxin is dissolved in about 5 c.c. of this glacial acetic acid containing iron oxide, and this solution is layered on to 5 c.c. of the sulphuric acid containing iron oxide, the coloration, especially the bluish-green band, will become more evident. The green coloration referred to above, formed by the action of concentrated hydrochloric acid on the glucoside, is also characteristic of digitoxin.

Digitonin is not coloured either by hydrochloric acid or by sulphuric acid in the cold. On boiling with hydrochloric acid, or with sulphuric acid which is not too dilute, a red solution results the intensity of which gradually increases. (Compare Cloetta, *Archiv für experimentelle Pathologie* 1901, Vol. 45, p. 435.)

The reactions given above suffice as a means of identification for pharmaceutical purposes; they are not conclusive for forensic purposes. In this case a biological examination is absolutely necessary.

Besides the qualitative tests, the quantitative estimation of digitalis glucosides in digitalis leaves is of more general interest. So far the estimation of digitoxin, as worked out by Keller, is the only one deserving of consideration. It can be applied in a slightly modified form in the following way.

28 grammes of air-dried, powdered digitalis leaves are placed in a suitable glass-stoppered flask of 500 c.c. capacity; over these are poured 280 grammes of alcohol 60 p.c. (by weight) and the mixture is left to stand for 3 to 4 hours, shaking it frequently. It is then filtered and 207 grammes of the filtrate are evaporated to about 25 grammes on a water-bath. Sufficient water is added to the residue to bring the total weight to 222 grammes, and while stirring, 25 grammes of official liq. plumbi subacetatis fort. are added. The mixture is immediately filtered and to 132 grammes of the filtrate, in an Erlenmeyer flask, a solution of 5 grammes of sodium sulphate in 8 grammes of water is added. When the precipitate has settled, 130 grammes of the clear fluid are poured into a separator, 2 grammes

of solution of ammonia (10 p.c.  $\text{NH}_3$ ) are added and the mixture is shaken 5 times, each time with 30 c.c. of chloroform. The chloroformic solutions are filtered and then evaporated, the dry residue is dissolved in 3 grammes of chloroform, and, in order to precipitate the digitoxin, 7 grammes of ether and 50 grammes of petroleum ether are added. The flocculent digitoxin which separates is collected on a small filter (5 cm. diameter) and dissolved on the filter by the addition of hot absolute alcohol. The alcoholic solution which runs through is collected in a glass capsule, evaporated to dryness and the residue dried until the weight is constant. This multiplied by 10 gives the percentage of digitoxin contained in the leaves analysed. But, according to J. Burmann, this so-called digitoxin is pseudodigitoxin, for in contradistinction to true digitoxin it is amorphous and soluble in water and ether. Kraft declares that the product obtained by Keller's method consists chiefly of gitalin (or gitalin hydrate and anhydrogitalin, in addition to digitoxin. He agrees with Burmann in that he also considers Keller's digitoxin to contain only a very small amount of digitoxin.

## 2. Physiological and Pharmacological.

It is generally acknowledged that digitalis represents a cardiac poison for cold-blooded and warm-blooded animals, the action of which can be produced equally by using a single large dose or by smaller doses continued for some time. This action affects the heart, the circulation, the central nervous system, metabolism and diuresis to a greater or less extent; it is also said to have a paralysing influence on the muscles and to disturb digestion. The action varies considerably according to the dose and to individual idiosyncrasy, so that the three usual stages in the action of digitalis may not be differentiated or may occur in unusual sequence, or not at all. The first stage consists in a decrease in the pulse rate and a rise in arterial blood pressure, symptoms due to direct stimulation of the vagus.

Burmann, Bulletin de la société chimique 1910, p. 973. — Chemiker-Zeitung 1911, Repert., p. 31.

Kraft, Schweizer Wochenschrift für Chemie und Pharmazie 1911, p. 174.

If the stimulation of the vagus be too strong, the second stage in the action of digitalis is reached — the paralysis of the vagus leads to a sudden considerable increase in the pulse rate and a gradual fall in blood pressure. The third stage is marked by a very high pulse rate and very low blood pressure, the heart is completely paralysed, stops in diastole and fails to respond to any further stimulant action. These three stages only occur in warm-blooded animals when the dose administered is suitable for the individual, and this cannot in all cases be determined beforehand. If the dose be too small, the action may not go beyond the first stage, and on the other hand, if the dose be too large, the action of the second or third stage is almost immediately displayed.

The action of digitalis on the central nervous system in man is apparent by vertigo, hallucinations, fainting, supraorbital neuralgia, buzzing in the ears, dilated pupils, and disturbances of vision. With regard to the action of digitalis on metabolism, von Böck has shown that it increases with a rise in blood pressure, while a fall in blood pressure causes a decrease in metabolism. Diuresis also appears to depend on the rise or fall of blood pressure, but in the normal, healthy individual it is little influenced by digitalis. In the presence of organic heart lesions, digitalis must be admitted to have a diuretic action.

Only the first of the three stages in the action of digitalis mentioned above, and first described by Traube, is of therapeutic importance; therefore the doses administered should be such as not to lead to the dangerous second stage, nor to the third stage, which ends fatally.

An important chapter in digitalis therapy, apart from the therapeutic action of the digitalis substances, deals with their by-effects, which are partly due to the action of the substances themselves and partly to their products of decomposition. In the internal administration of digitalis, or digitalis glucosides, they generally take the form of vomiting or diarrhoea; in their external application, as injections, they take the form of symptoms of local irritation. These by-effects are occasionally observed as a consequence of too large doses, individual idiosyncrasy, or as the result of using decomposed preparations, when using digitalis leaves or

galenical preparations of the latter, or digitalis glucosides. Thus even when the purest glucosides are used, these by-effects may occur. But in by far the greater number of cases they are due to products of decomposition, which are formed either in the drying of the digitalis leaves or in the manufacture of the individual preparations. Digitaliresin and toxiresin especially, as was pointed out by Perrier, have an unpleasant action, which is liable to produce convulsions.

One of the unwelcome by-effects of digitalis substances is the so-called cumulative action, a property shared, without exception, by all the active digitalis substances. It has sometimes been stated in the literature that one or other of the digitalis preparations lacked the cumulative action, this statement cannot, however, be unconditionally accepted. At first, either from too great enthusiasm or for speculative reasons, cumulative properties were denied for all the preparations, until experimental evidence disproved this statement. But not every worker in this field can be accused of inaccurate observation, for most of them were not in a position to test the digitalis preparation they were using for the active substances it contained. For instance, anyone who tested clinically a preparation containing 10 p.c. of digitoxin and 90 p.c. of inactive or only slightly active substances could easily draw the conclusion that he was dealing with a preparation which was only slightly poisonous and possessed no cumulative action, at any rate when compared with pure 100 p.c. digitoxin; and he might easily overlook the fact that its action was also very much weaker. This does not imply that the therapeutic effect and cumulative action are always definitely and unalterably proportionate, for in this respect the individual idiosyncrasy of the patient is an important factor, but it may safely be inferred that weak preparations have often led to the conclusion that the preparation had only a slight cumulative action, more especially when the patients reacted well to comparatively small doses. In order to speak of a relative cumulative action it must be proved that in giving equally effective doses of the three digitalis substances recognised as active, viz., digitalin, digitalein and digitoxin, one of them shows stronger or weaker cumulative effects than the other. No one has as yet suc-

Perrier, *Archiv für experimentelle Pathologie und Pharmakologie* 1875, Vol. 4, p. 191.

ceeded in adducing this proof. Rather it must be acknowledged that these three substances are so similar in qualitative action that our means for distinguishing between them physiologically or pharmacologically are insufficient, and that they all possess a cumulative action which cannot be denied. Therefore the therapist must always reckon with this fact, no matter which preparation of digitalis he uses. Action on the heart and cumulative action are two inseparable attributes in the pharmacology of digitalis. The conception of cumulative action is not easy to define, as it includes not only the stronger action of the last doses of digitalis, but also the relatively early appearance of the action following upon equally large or smaller initial doses. Further, it must be borne in mind that this action can be displayed in a therapeutic as well as in a toxic form, and the therapeutic and toxic cumulative action may be considered identical. The commencement of cumulative action is usually considered to occur when the excretion of the medicament takes place quantitatively more slowly than its ingestion, so that an accumulation (*cumulatio*) takes place in the organism, or, as appears to be the case with digitalis substances, in the heart or the cardiac muscle. This accumulation gives rise to a stronger action of the succeeding doses of digitalis, but the accumulated mass of digitalis substances cannot always be taken as the standard, for the heart appears to react more energetically to fresh doses for a time after all fixed digitalis glucosides have been excreted. According to this, a cumulative action is conceivable and possible, even apart from the summation of the mass of material stored in the heart, or of its action. (Lhotak von Lhota, *Archiv für experimentelle Pathologie und Pharmakologie*, 1908, Vol. 58, p. 350.)

In practice the cumulative action is obviated by ceasing the administration of digitalis substances immediately on the appearance of its symptoms, and discontinuing the treatment for a few days, when it may be recommenced with smaller doses, if necessary. A change to the use of bodies belonging to the so-called digitalin group, to which have recently been reckoned substances not derived from digitalis, e. g., strophanthin, helleborein, convallamarin, adonidin, etc., is not always successful in preventing cumulative symptoms, for it has been found that strophanthin, for

example, when given after digitoxin or digitalin, also gives rise to cumulative action and its consequences. Therefore a change of medication, as for instance from the internal administration of digitalis to the intravenous injection of strophanthin, requires care.

For a more detailed description of the physiological and pharmacological action of the digitalis substances and of digitalis itself the following literature should be consulted:

- Traube, Über die Wirkungen der Digitalis, insbesondere über den Einfluß derselben auf die Körpertemperatur in fieberhaften Krankheiten. *Annalen des Charité-Krankenhauses* Vol. 2, p. 19.
- Winogradoff, Pharmakologie des Digitalins. Einwirkung auf den Stoffwechsel. *Virchows Archiv* Vol. 22, p. 457.
- Hirtz, Wirkung der Digitalis auf Fiebererscheinungen. *Journal de pharmacie* 1862, I, p. 428.
- Böhm, Wirkung der Digitalis und des Digitalins. *Pflügers Archiv der Physiologie* 1872, Vol. 5, p. 158.
- Böhm (Görz), Digitalin Native in chemischer und physiologischer Beziehung. *Archiv für experimentelle Pathologie* 1874, Vol. 2, p. 123.
- Ackermann, *Archiv für klinische Medizin* Vol. 9, p. 125.
- Schmiedeberg, Untersuchungen über die pharmakologisch wirksamen Bestandteile der Digitalis purpurea. *Archiv für experimentelle Pathologie* 1875, Vol. 3, p. 16, 1883, Vol. 16, p. 162.
- Fraenkel, Tonographische Untersuchungen über Digitaliswirkung. *Archiv für experimentelle Pathologie* 1889, Vol. 40, p. 40.
- Gottlieb und Magnus, Über die Gefäßwirkung der Körper der Digitalisgruppe. *Archiv für experimentelle Pathologie* 1902, Vol. 47, p. 135.
- Benedicenti, Über die Wirkung der Digitalisstoffe bei exkordialer Applikation. *Archiv für experimentelle Pathologie* 1902, Vol. 47, p. 360.
- Cloetta, Zur Kenntnis der Darstellung und Zusammensetzung der Digitalisglykoside. *Archiv für experimentelle Pathologie* 1898, Vol. 41, p. 421, 1901, Vol. 45, p. 368. — Über das Verhalten des Digitoxins im Organismus, *ibidem* 1906, Vol. 54, p. 294. — Über den Einfluß der chronischen Digitalisbehandlung auf das normale und pathologische Herz, *ibidem* 1908, Vol. 59, p. 209.
- Jacoby, Zur Physiologie des Herzens unter Berücksichtigung der Digitaliswirkung. *Archiv für experimentelle Pathologie* 1900, Vol. 44, p. 368.
- Schliomensum, Über die Bindungsverhältnisse zwischen Herzmuskel und Digitalis (Digitoxin). *Archiv für experimentelle Pathologie* 1910, Vol. 63, p. 294.
- Markwalder, Zur Physiologie und Pharmakologie der Diastole. *Archiv für experimentelle Pathologie* 1910, Vol. 63, p. 38.
- Fraenkel, Vergleichende Untersuchungen über die kumulative Wirkung der Digitaliskörper. *Archiv für experimentelle Pathologie* 1904, Vol. 51, p. 84.

- Loeb, Über die Beeinflussung des Koronarkreislaufes durch einige Gifte (Digitoxin, Strophanthin). Archiv für experimentelle Pathologie 1904, Vol. 51, p. 69.
- Herzig, Leukozytose unter Einwirkung der Digitalis. Archiv für experimentelle Pathologie 1905, Vol. 53, p. 157.
- Schwartz, Zur Kenntnis der Behandlung akuter und chronischer Kreislaufstörungen. Archiv für experimentelle Pathologie 1906, Vol. 54, p. 141.
- Recklinghausen, Wirkung der Digitaliskörper beim herzkranken und herzgesunden Menschen und beim Tiere. Archiv für experimentelle Pathologie 1907, Vol. 56, p. 40.
- Lhotak von Lhota, Untersuchungen über die vaguslähmende Wirkung der Digitaliskörper. Archiv für experimentelle Pathologie 1908, Vol. 58, p. 350.
- Loewi, Über eine spezifische Nierenwirkung der Digitaliskörper. Archiv für experimentelle Pathologie 1908, Vol. 59, p. 71.
- Plumier, Action de la Digitoxine, de la Digitaline et de l'alcool sur la circulation cardio-pulmonaire. Journal de physiologie 1905, p. 455.
- Herzog, Leukozytose unter Einwirkung von Digitoxin und Digitalin. Archiv für experimentelle Pathologie 1905, Vol. 53, p. 157.
- Friedländer, Therapeutische Monatshefte 1907, No. 4.
- Fahrenkamp, Über die verschiedene Beeinflussung der Gefäßgebiete durch Digitoxin. Archiv für experimentelle Pathologie 1911, Vol. 65, p. 367.

### 3. Therapeutical.

#### Digitoxin.

Digitoxin, which represents the most active principle of digitalis leaves\*), is the most trustworthy glucoside of digitalis, as it can be prepared in a very pure form owing to its property of forming crystals. The reason why it has not been more appreciated, and has so far only been included in two pharmacopoeias — the Pharmacopoea Helvetica and the Pharmacopée Française — is probably due to the fact that it is almost insoluble in water and is considered a relatively very toxic digitalis substance. This, however, should not prevent its more general use, seeing that it shares this property with various other official poisons\*\*). It has

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\*) Arnold, Wood, American Journal of Medical Sciences 1900, Vol. 120, p. 165.

\*\*) Compare: Koppe, Archiv für experimentelle Pathologie, Vol. 3, p. 274.

Lauder Brunton, Gazette des hôpitaux 1900, p. 992, Lancet 1900, 18th Aug., p. 477.

received such many-sided recognition that it can be recommended for more extensive therapeutic trial.

Digitoxin is indicated in all cases in which digitalis has been found of use, especially in diseases of the heart, such as valvular insufficiency and mitral stenosis, and also in nephritis, pneumonia, typhoid, etc.

The first exhaustive clinical test of pure digitoxin was carried out by Masius, who was so well satisfied with his results that he warmly recommended its further therapeutic use. In his experience, the action of digitoxin in broken down or insufficient compensation is certain, rapid, and energetic, without causing gastric disturbances of any moment. As a rule the action is evident in 24 hours, or even in 12 hours; cyanosis and respiratory disturbances disappear, the pulse becomes stronger and more regular, diuresis is increased, oedema disappears and the general condition is improved. The action usually lasts for 8 to 10 days. In pneumonia and typhoid, Masius also observed a favourable effect on the pulse and temperature. In Graves' disease the tachycardia was favourably influenced. Masius made use of the following prescription:

Rp. Digitoxin Merck	0.1 gramme ( $1\frac{1}{2}$ grains)
Spirit. vin.	205.0 grammes ( $6\frac{5}{6}$ oz)
Aq. destill.	740.0 grammes ( $24\frac{2}{3}$ oz)
Sacchar.	55.0 grammes ( $1\frac{5}{6}$ oz)

Of this 0.01 p.c. solution 15 grammes ( $\frac{1}{2}$  oz) are mixed with 25 grammes ( $\frac{5}{6}$  oz) of syrup and given every 4 hours. A single dose therefore contains 0.0005 gramme ( $\frac{1}{125}$  grain) and a daily dose 0.0015 gramme ( $\frac{1}{40}$  grain).

Corin, who has carried out more thorough clinical tests with digitoxin than has any other investigator, also considers this drug to be the most valuable of the digitalis glucosides, surpassing by far the French crystalline digitalin

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Lafon, Annales d'hygiène publique (3) Vol. 16, p. 506.

Braun, Mager, Sitzungsberichte der Math. naturwiss. Classe, Vienna 1900, Vol. 108, III, p. 471.

Zeltner, Münchener medizinische Wochenschrift 1900, p. 886.

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Masius, Bulletins de l'académie de médecine de Belgique 1893 and 1894. — Semaine médicale 1894, p. 315.

Corin, Le Scalpel 1895, 14<sup>th</sup> April. — Therapeutische Wochenschrift 1895, p. 673.

(Nativelle). In opposition to Bardet he pointed out that, apart from the necessity of administering digitoxin in solution, it was of importance to ensure that the dissolved digitoxin should not become insoluble when coming into contact with the body juices. He believes that the non-observance of this consideration affords an explanation of the different action of digitoxin observed by others. He therefore prescribed the following solution, which is not precipitated by water, physiological salt solution, or by serum:

Rp. Digitoxin Merck	0.003 gramme	( $\frac{1}{20}$ grain)
Chloroform.	1.0	gramme (12 min.)
Spirit. vini.	1.0	gramme (20 min.)
Aq. destill.	ad 200.0	grammes ( $6\frac{2}{3}$ oz)

Sig. To be taken in three doses at intervals of 6 to 8 hours.

This medication gave good results in pneumonia. In the course of 15 years' experience Corin continued the use of digitoxin, and confirmed its usefulness, especially in large doses. In the author's experience the administration of digitoxin should be begun immediately the diagnosis of pneumonia has been made, because by this means the disease, provided it has not declared itself, can usually be cut short. At any rate digitoxin is effectual in bringing about the crisis several days earlier. This effect can usually be produced more easily by giving one comparatively large dose than by a succession of smaller doses. Following the administration of the drug, the author soon observed a fall in the temperature. But he attaches more importance to the fact that under the influence of digitoxin the pulse very soon becomes fuller, slower and stronger. In his opinion the action of the drug depends upon the rapidity of the absorption of the pulmonary exudate, whereby the nutrient medium for the pneumococci is removed. For this reason the action of the drug is only specific in croupous pneumonia, while in broncho-pneumonia following upon measles it is not apparent. Likewise the action is less evident in drinkers, a fact which has long been known with regard to other digitalis substances. From the large number of case histories given by the author one case only will be quoted, which places the action of digitoxin in a very favourable light.

Bardet, *Nouveaux remèdes* 1895, p. 27.

Corin, *Le Scalpel et Liège Médical* 1909, p. 291, 315, 331.

He gave his own 8 year old child 0.003 gramme ( $\frac{1}{20}$  grain) of digitoxin within a period of 40 hours, with the result that the pulse and temperature became perfectly normal on the third day. From the author's statistics it is seen that in over 600 cases the mortality was only 5.4 p.c.; for adults the mortality is somewhat higher. If we leave out of count those patients who were unable to take the digitoxin, e. g., who vomited immediately (6 out of 277), and one who was moribund when treatment was commenced, the mortality for adults is 9.5 p.c.; and it must be noted that about half of those who died were alcoholics. In 154 cases in which the commencement of the illness could be definitely determined, 32 were cured in 3 days, 52 in 4 days, 38 in 5 days, 21 in 6 days, and 11 in 7 days. The pulse and temperature in most of the cases returned to normal much earlier. With such excellent results Corin is justified in recommending further trials with large single doses of digitoxin instead of using small doses. The author suggests the following as the most suitable prescription:

Rp. Digitoxin cryst. Merck 0.003 gramme ( $\frac{1}{20}$  grain)  
Chloroform                      gutt. I—II  
Alcohol                          1 c. c. (17 min.)  
Aq. destill.                      50.0 grammes ( $1\frac{2}{3}$  oz)  
Vini albi  
Syrup. capill. Ven. aa 25.0 grammes ( $\frac{5}{6}$  oz)

This mixture is given to an adult in one dose at the commencement of treatment, and it should be given as cold as possible. The patient should have eaten nothing for at least an hour before taking the dose; he should lie as flat as possible with the head only slightly raised, and he should drink nothing for an hour afterwards. If there be any inclination to vomit, ice should be applied to the epigastrium. The emptier the stomach, the more promptly is digitoxin said to act. If vomiting only supervenes after an hour, this does not usually interfere with the action.

With regard to the dosage\*), the following points should be considered: For an adult man at least 0.003 gramme

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\*) Up to the present the maximum single dose was given as 0.001 gramme ( $\frac{1}{64}$  grain) and the maximum daily dose as 0.003 gramme ( $\frac{1}{20}$  grain). Corin's dosage appears less striking when we consider that the action of the drug only develops in the course of 12 to 24 hours, and for this reason, and on

( $\frac{1}{20}$  grain) should be given at the commencement of the illness. If the case is somewhat advanced and the temperature is high, strong persons and alcoholics are given 0.004 to 0.0045 gramme ( $\frac{1}{16}$ — $\frac{1}{14}$  grain) or even 0.005 gramme ( $\frac{1}{12}$  grain), especially if no good result is apparent 24 hours after the first dose. For children over 10 years of age the dose at the commencement of the illness should be at least 0.0025 gramme ( $\frac{1}{25}$  grain); for those under one year 0.0003 to 0.001 gramme ( $\frac{1}{200}$ — $\frac{1}{64}$  grain), and after the pneumonia has started 0.001 gramme ( $\frac{1}{64}$  grain) should be given within 24 hours, or in one dose; on the following days 0.0005 to 0.001 gramme ( $\frac{1}{125}$ — $\frac{1}{64}$  grain) is administered. For children of 1 to 2 years a single dose of 0.001 gramme ( $\frac{1}{64}$  grain) is occasionally sufficient, but sometimes 0.0013—0.002 gramme ( $\frac{1}{50}$ — $\frac{1}{32}$  grain), given within 12 to 24 hours is required. To children of 2 to 3 years of age 0.001—0.0015 gramme ( $\frac{1}{64}$ — $\frac{1}{40}$  grain) is given within 24 hours at the commencement of the illness, and after the disease has started 0.0018 to 0.002 gramme ( $\frac{1}{36}$ — $\frac{1}{32}$  grain). To children of 5 to 10 years of age about the same dose may be given as to adult women. For these the author prescribes on an average 0.0025 gramme ( $\frac{1}{25}$  grain) at the beginning of the illness.

The conclusions arrived at by Corin as a result of his 15 years' experience are as follows: Digitoxin acts best at the commencement of pneumonia. By administering large doses the disease can be cut short, provided it is not too far advanced and the patient's system is not overloaded with toxins. The action of digitoxin in pneumonia following upon measles is nil. It is, however, useful in these cases if given as a heart tonic. But it will not effect a cure of broncho-pneumonia due to measles. Like all heart tonics and most nerve tonics, digitoxin does not act so well in alcoholics.

Corin's favourable report is of particular interest, as the value of digitoxin and of digitalis generally in pneumonia was beginning to be doubted by other authors.

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account of the cumulative properties of the glucoside, it appears immaterial whether the maximum daily dose be given once in one dose or in several smaller doses. Besides, much larger doses are now given of other substances belonging to the digitalis group, e. g., strophanthin, so that the doses suggested here cannot be considered alarmingly large. In view of the author's long experience, we may safely rely upon his statements.

Unverricht and Wenzel have also expressed themselves well satisfied with the value of digitoxin. They state that the preparation, besides being taken internally, may also be given subcutaneously, and especially rectally, with great benefit. By the administration of the medicament as an enema, the digestive disturbances which are likely to occur with all digitalis preparations can be considerably diminished or totally avoided, without interfering with the powerful action of digitoxin on the heart. According to Wenzel, a good result can be obtained by this treatment in myocarditis and valvular disease, even if infusion of digitalis has failed. Wenzel prescribes digitoxin in the following solution:

Rp. Digitoxin Merck	0.01 gramme ( $\frac{1}{6}$ grain)
Spirit. vini	10.0 grammes ( $\frac{1}{3}$ oz)
Aq. destill.	ad 200.0 grammes ( $6\frac{2}{3}$ oz)

Of this solution, after rectal lavage, 15 grammes ( $\frac{1}{2}$  oz) mixed with 100 grammes ( $3\frac{1}{3}$  oz) of lukewarm water were given rectally at first 3 times a day, then twice and finally once a day. Thus the patient received 0.00075 gramme ( $\frac{1}{80}$  grain) of digitoxin in each dose. With this method the author observed vomiting only in two cases, and it ceased immediately on the discontinuance of the medicine. But these patients had complained of gastric trouble before taking digitoxin and were debilitated as a consequence of their prolonged heart disease. The other patients, without exception, bore the enemata without disturbance.

In order to render the administration of digitoxin more convenient, I supply the preparation in tablet form, each tablet containing 0.00025 gramme ( $\frac{1}{250}$  grain) of digitoxin, these are soluble in lukewarm water containing alcohol (15 drops of alcohol to 100 grammes ( $3\frac{1}{3}$  oz) of water). For an enema 2 tablets are used on an average.

These tablets, according to Unverricht, are also suitable for internal use. By the administration of one tablet every 3 hours, or in less urgent cases by the use of 3 to 4 tablets a day, the desired result is obtained. The tablets may be swallowed whole, but they are absorbed better if they are first dissolved in water containing alcohol.

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Unverricht-Wenzel, Zentralblatt für innere Medizin 1895, No. 19, p. 458.

Unverricht, Deutsche Ärzte-Zeitung 1895, No. 22.

Unverricht has also prescribed digitoxin subcutaneously in the following solution:

Rp. Digitoxin Merck	0.01 gramme ( $\frac{1}{6}$ grain)
Alcohol. absolut.	5.0 grammes (100 min.)
Aq. destill.	15.0 grammes ( $\frac{1}{2}$ oz)

Sig. 0.5 to 1 c.c. (8—17 min.) to be injected.

Kaufmann and Koppe have pointed out that digitoxin, when given subcutaneously, may cause great irritation, or even phlegmon or aseptic suppuration. By using the above solution phlegmon is never observed and there is either no irritation of the connective tissue, or if present, it is very slight. Van Aubel denies that digitoxin has any irritant properties and recommends its use, dissolved in a little alcohol or chloroform and mixed with water, for intravenous injection. For intravenous injections a solution of 0.0015 gramme ( $\frac{1}{40}$  grain) of the preparation in a little chloroform and 150 c.c. (5 oz) of water may be used, of which 12.5 c.c. (210 min.) may be given as a dose, corresponding to 0.000125 gramme ( $\frac{1}{500}$  grain) of digitoxin. In order to avoid the precipitation of digitoxin in the stomach and consequent gastric trouble, he prescribed a solution of 0.003 gramme of digitoxin in 10 grammes of chloroform and 200 grammes of water, or a solution of 0.0015 to 0.002 gramme of digitoxin in 10 grammes of alcohol and 200 grammes of water, a corresponding amount of which was given. The author also considers that the toxicity of digitoxin, determined by other observers, has been exaggerated, for in experiments on animals only comparatively large doses are fatal.

Huchard prescribed for subcutaneous injection a solution of 0.02 gramme of digitoxin in 2 grammes of chloroform, 26.5 grammes of alcohol and 48 grammes of water; Barié a solution of 1 gramme of digitoxin in 250 grammes of alcohol and 250 grammes of water; Meunier a solution of 0.01 gramme of digitoxin in 1 gramme of chloroform and 5 grammes of liquid paraffin, or a solution of 0.003 gramme of digitoxin in 6 grammes of chloroform, 7 grammes of alco-

Kaufmann, Archiv für experimentelle Pathologie Vol. 25, p. 397.

Koppe, Archiv für experimentelle Pathologie 1875, Vol. 3, p. 274.

Aubel, Bulletin de l'académie de médecine de Belgique 1894.

— Travaux thérapeutiques expérimentales de Liège Vol. 1, p.

337. — Semaine médicale 1893, p. 147, 231 and 1894, p. 507.

Huchard, Barié, Meunier, Rosenthal, Presse médicale 1902, p. 367.

hol and 293 grammes of physiological salt solution; and Rosenthal a solution of digitoxin in oil. The author at first suggested a solution containing 0.000125 gramme of digitoxin in 1 c.c. of sterile olive oil, but more concentrated solutions can be prepared. The oily preparations are said to possess the great advantage of being only slightly irritant, or entirely painless.

The communications of Dejardin, H. Wolf and Collard agree with Corin's results. These authors lay special stress upon the use of digitoxin in the congestive period of pneumonia and in post-operative pneumonia, but it must be remembered that a period of at least 9 hours elapses before the action of digitoxin is fully developed, so that the preparation must be given in good time.

Fiessinger declares digitoxin to be an excellent remedy for the treatment of cardiac sclerosis with or without nephritis, but it must only be given in very small doses in these cases. The author has frequently given it for periods of 10 days at fortnightly intervals. He prescribes it as follows:

Rp. Solutionis alcoholic. digitoxini (1:1000) gtts. V

Aq. destill. 300.0 grammes (10 oz)

Sig. One tablespoonful to be taken at 10 a.m. and at 4 p.m., so that the mixture will last for 10 days.

This dosage should under no circumstances be increased, even if in consequence of valvular lesions or of the previous administration of larger doses the desired result is not obtained, for otherwise it may have unpleasant effects on the heart muscle.

In mitral stenosis Petit has given small doses of digitoxin with good effect. He prescribed 5 drops of an alcoholic solution 1:1000 to be given for 3 to 4 days every month and only permitted larger doses to be given if no unpleasant by-effects were observed. If asystole should occur, the drug may be given in small daily doses.

According to Curioni, the action of digitoxin in myocarditis can be observed in 4 to 5 hours; the quality of

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Dejardin, *Le Scalpel* 1896, p. 193.

Wolf, *Ärztliche Mitteilungen aus und für Baden* 1896, p. 169.

Collard, *Le Scalpel* 1896, p. 210.

Fiessinger, *Revue internationale de médecine* 1903, p. 386.

Petit, *Progrès médicale* 1911, 4<sup>th</sup> March.

Curioni, *Clinica medica italiana* 1901, No. 11.

the pulse is improved and the arterial pressure is considerably increased. The dicrotism of the pulse disappears with doses of 0.0005 gramme ( $\frac{1}{125}$  grain) while with doses of 0.00075 gramme ( $\frac{1}{80}$  grain) a more or less definite increase in the blood pressure may be expected. In chronic heart disease the author suggests 0.001 gramme ( $\frac{1}{64}$  grain) as the maximum daily dose, which is said not to cause dangerous by-effects.

The gastric disturbances observed by I. P. Arnold and H. C. Wood and others as a result of the internal administration of digitoxin are certainly not the rule, otherwise they would not have been partially or wholly denied by such a large number of authors. The question arises what is to be done if a patient vomits after taking digitoxin or digitalis infusion, for in these cases, apart from harassing the patient, its action is open to doubt. In opposition to Corin (compare above), Penzoldt recommends that the digitoxin should be taken after meals in these cases. Another way out of the difficulty is to give the preparation subcutaneously, intravenously, or rectally. Several papers may be cited with reference to this point.

Hoffmann von Wellenhof gives his opinion on digitoxin in the following words:

"1. Although for the present the use of the plant itself cannot be left out of consideration, yet the prejudice against the use of pure constituents of digitalis at the bedside must be limited. The undeniable drawbacks which are cited, especially with regard to the practical use of digitoxin, appear to be compensated by the rapid and well defined manner in which very small doses call forth the characteristic action of digitalis. In some respects it would appear that digitoxin is superior to the infusion as regards the speedy onset and intensity of cardiac action.

2. Single and daily doses should be as small as the circumstances of the individual case will permit. It is never necessary to exceed a daily dose of 0.002 gramme ( $\frac{1}{32}$  grain). The total amount of digitoxin used (during the whole period of treatment) should not exceed 0.005 gramme ( $\frac{1}{12}$  grain) subcutaneously, and 0.007 gramme ( $\frac{1}{8}$  grain) rectally.

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Arnold-Wood, American Journal of Medical Sciences 1900, p. 165.

Penzoldt, Gazzetta internazionale di Medicina pratica 1900, No. 8 and 9.

Wellenhof, Wiener klinische Wochenschrift 1896, No. 42.

3. As subcutaneous injection is somewhat painful, the application by enemata will usually be preferable. A special indication for the former method is the necessity of obtaining the digitalis action as quickly as possible.

4. The most important contra-indication (apart from severe degenerative changes of the heart muscle) is the presence of severe gastric disturbances.

5. Digitoxin should be given to children only with the greatest care."

Biedert reports a case of myocarditis and dropsy, in which all the usual drugs, such as digitalis, strophanthin, diuretin and sparteine had been tried in vain, whereas subcutaneous injections of digitoxin yielded good results.

The reason why digitoxin is but little used subcutaneously lies in its insolubility in water. When alcohol is used, as appears from the reports of Hoffmann von Wellenhof and other authors, the injections are painful, and for this reason other solvents have been sought. Madsen considers the so-called Petit's liquor to be a suitable solvent for digitoxin. It is prepared by mixing 333 grammes of glycerin with 147 grammes of water and sufficient alcohol (95 p. c.) to make the specific gravity of the mixture equal to that of water, e.g., 1.00\*). If 1 gramme of digitoxin is dissolved in 1 litre of this mixture, a clear solution is obtained, which will keep well, and of which, according to Allard, 37 to 40 drops correspond to 0.001 gramme of digitoxin. Either by itself or mixed with water in suitable proportions, this solution is certainly useful for subcutaneous and rectal use; no reports, however, on its use in practice have come to my knowledge.

In any case the solution of digitoxin mentioned above can be used internally and rectally, as is apparent from the communications of Allard. The author obtained the best results in cases of cardiac sclerosis and in the milder cases of cardiac degeneration with œdema, and also in cases of

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Biedert, Merck's Reports 1896, p. 53.

Madsen, Merck's Reports 1900, p. 85 and 1902, p. 51.

\*) Petit's liquor is best prepared by mixing 100 grammes of glycerin, 44 grammes of water and 106 grammes of alcohol (96 p. c.). If the digitoxin is dissolved in alcohol, and glycerin and water are then added, there will be no difficulty in dissolving the digitoxin.

Allard, Hygiea 1900, Vol. 5.

mitral and aortic valvular lesions, and in hypertrophy and dilatation of the ventricle, the result of emphysema and chronic bronchitis. In recent cases of myocarditis, endocarditis and pericarditis the results were unequal, and in nephritis, œdema and Graves' disease the author was unable to detect any noticeable action of the drug. When applied rectally the action, according to Allard, takes place later, in fact not for 24 to 48 hours. Allard is very careful with the dosage. He considers 0.001 gramme ( $\frac{1}{64}$  grain) too much, especially if cardiac degeneration or fever is present. He is of opinion that in advanced degeneration the dose should not exceed 0.00025 gramme ( $\frac{1}{250}$  grain). According to J. Sawyer, doses of 0.000125 to 0.00025 gramme ( $\frac{1}{500}$ — $\frac{1}{250}$  grain) should suffice, and by using such small doses by-effects are better avoided. He also states that by this method the subcutaneous and rectal administration can be dispensed with. As these sometimes cause difficulties, E. Zeltner is also in favour of oral administration. Although it does not act so promptly, its action is just as sure as that of subcutaneous injection. On the whole Zeltner has come to the same conclusions as Unverricht and Wenzel with regard to the therapeutic value of digitoxin, namely that it is not inferior to the use of digitalis leaves, either in rapidity or potency of action, and has the advantage of more exact dosage. It also possesses another advantage over digitalis leaves and over the so-called standardised leaves, viz., that it does not decompose on keeping, so that on using a preparation which has been kept for a time there is not the risk of finding a considerable diminution in action, as may be the case with digitalis leaves. Clinicians are gradually becoming convinced that digitoxin represents the most active and also the most convenient constituent of digitalis\*).

With regard to the maximum doses of digitoxin, it is not possible at present to give reliable data on this point. The

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Sawyer, Journal of the American Medical Association 1899, 28<sup>th</sup> October.

Zeltner, Münchener medizinische Wochenschrift 1900, p. 886.

\*) This opinion is also expressed in the communications of Salomon (New York Medical Journal 1901, 9<sup>th</sup> February) and of Bosse (St. Petersburg Medical Journal 1901, p. 51), and in the proceedings of the 19<sup>th</sup> Congress of International Medicine in Berlin (Berliner klinische Wochenschrift 1901, p. 465 or Semaine médicale 1901, p. 129).

Pharmacopœa Helvetica and the Pharmacopée Française suggest as a maximum single dose 0.0003 gramme ( $\frac{1}{200}$  grain), and as a maximum daily dose 0.001 gramme ( $\frac{1}{64}$  grain); Liebreich and Langgaard (Kompendium der Arzneiverordnung 1907, p. 253) fix the maximum single dose at 0.0005 gramme ( $\frac{1}{125}$  grain) and the maximum daily dose at 0.0015 gramme ( $\frac{1}{40}$  grain) and they state that the total amount given during the period of treatment should not exceed 0.007 gramme ( $\frac{1}{10}$  grain). Kobert (in his Arzneiverordnungslehre 1900, p. 334) suggests a maximum single dose of 0.002 gramme ( $\frac{1}{32}$  grain), and a maximum daily dose of 0.004 gramme ( $\frac{1}{16}$  grain), and as the initial dose 0.0004 gramme ( $\frac{1}{160}$  grain). (Compare also p. 61.)

### Digitalinum (purum pulv.) Germanicum.

The German (amorphous) digitalin has always been a favourite preparation, because it is soluble in water and therefore convenient in use. As a cardiac tonic and a diuretic it acts like digitalis leaves, and can therefore be used in the same way when indications for digitalis arise. It is prescribed internally or subcutaneously, in aqueous solution, and in single doses of 0.005 to 0.02 gramme ( $\frac{1}{12}$ — $\frac{1}{3}$  grain). The maximum daily dose is fixed at 0.03 gramme ( $\frac{1}{2}$  grain)\*.

The favourable manner in which digitalinum Germanicum has been criticised is best apparent in the communications of J. M. Patton, G. O. Jarvis, S. Cohen and Beates. An extract of the experimental results obtained by the latter, which almost entirely agree with those of the other authors named, is given below.

Beates mentions as a specially important property of digitalinum Germanicum Merck the absence of unpleasant by-effects on the digestive tract, a circumstance of considerable weight in advanced heart disease, in which large doses are necessary. Only when using large doses such as 0.02 to 0.03 gramme ( $\frac{1}{3}$ — $\frac{1}{2}$  grain) has the author occasionally noti-

\*) The doses formerly cited in the literature (compare Merck's Index), e. g., 0.001—0.004 gramme ( $\frac{1}{64}$ — $\frac{1}{16}$  grain), are too small, according to the American authors mentioned above.

Patton, Philadelphia Medical Journal 1902, p. 1105.

Jarvis, International Medical Magazine 1902, Vol. 11, p. 22.

Cohen, Philadelphia Medical Journal 1902, p. 1105.

Beates, Journal of the American Medical Association 1897, p. 1209, 1898, p. 761 and 1907, p. 70.

ced the occurrence of slight gastric disturbances. For this reason he fixed the maximum dose at 0.03 gramme ( $\frac{1}{2}$  grain), while he considers 0.006 gramme ( $\frac{1}{10}$  grain) to be the smallest active dose. But even should gastric disturbances supervene when large doses are given, they can be cured by the administration of peptone and hydrochloric acid combined with a bitter tonic, or of a preparation of bismuth, and thus permit the continuation of the digitalin medication.

In all abnormal heart symptoms digitalin. Germanicum is of the utmost service and it is therefore to be preferred to other official preparations of digitalis. It always acts promptly, except in valvular disease combined with dilatation of the valves.

Digitalin. Germanicum is of special service in senility, in which the most prominent symptoms are congestion, general debility, dyspnoea after slight exertion, spasmodic cough, forgetfulness and lethargy. In these cases the administration of 0.01 to 0.02 gramme ( $\frac{1}{6}$ — $\frac{1}{3}$  grain) of digitalin. Germanicum is said to cause the disappearance of the symptoms in a short time and to bring about the return of normal conditions, which may lead to a complete cure. In more advanced old age, marked by calcification and degeneration of the arteries, by occasional mental confusion, temporary loss of speech and paralyses, digitalin, in Beates' experience and in opposition to the opinion of other authors, is a useful drug, for according to his careful observations, it strengthens the weakened heart, increases the vaso-motor tone, makes the absorption of nourishment possible, regulates metabolism and so prolongs life. In several patients who had suffered severely before, the preparation is said to have warded off all symptoms for 3 years. If albuminuria be added to the symptoms of old age mentioned above, the regular use of digitalin brings about an improvement in the general state of health and strength, which places the value of the drug in the most favourable light, on account of the weakness caused by the loss of albumin. Furthermore, Beates points out that by the use of digitalin the early stage of primary degeneration of the cerebral cortex can be arrested for some time. Muscular asthenia and motor symptoms are improved, even in patients who show no noticeable improvement in cardiac resisting power; the crisis of acute infective diseases, such as that of acute pneumonia, is better borne with digitalis. In

two cases of this kind Beates gave 0.12 gramme (2 grains) of digitalin. Germanicum Merck within two hours.

According to Jarvis, doses of 0.006 to 0.015 gramme ( $\frac{1}{10}$ — $\frac{1}{4}$  grain) of digitalin. Germanicum, even when given for many months, do not incommode the stomach in the least. The stimulating influence displayed by the preparation on the walls of the veins, on the cardiac muscle, the small blood vessels and the corresponding organs is very evident. This direct and reliable action contrasts markedly with the activity of digitalis leaves.

### Digitalinum Verum.

Digitalinum verum is only slightly soluble in water, but is soluble in dilute alcohol. Following B ö h m's pharmacological investigation of digitalin, M o t t e s tried the action of the preparation in man, and found that the best results were obtained by giving 0.00025 gramme ( $\frac{1}{250}$  grain) every 2 to 3 hours, when no unpleasant or dangerous symptoms appeared. According to Z i e m s s e n, digitalin has also been used with success in the Munich hospital. More detailed communications regarding the results of the investigations of these authors have not been published. There are also the two contradictory papers of F. P f a f f and K l i n g e n b e r g. Pfaff carried out his experiments with the aid of Jaquet's sphygmochronograph and came to the conclusion that digitalinum verum was identical in action with digitalis. As was at first stated with reference to every digitalis glucoside, the author was unable to detect any cumulative action when the preparation was administered internally. It also caused no vomiting and only gave rise to diarrhoea in persons usually disposed to diarrhoea. It may be given in the form of pills, or in solution in dilute alcohol in the form of drops, in which way it is more rapidly absorbed. According to the author, a daily dose of 0.008 to 0.016 gramme ( $\frac{1}{8}$ — $\frac{1}{4}$  grain), or even of 0.048 gramme ( $\frac{3}{4}$  grain) may be given, without the fear of toxic symptoms supervening\*).

Böhm, Archiv der Pharmazie 1892, Vol. 230, p. 258.

Mottes-Ziemssen, Archiv der Pharmazie 1892, Vol. 230, p. 259.

Pfaff, Korrespondenzblatt für Schweizer Ärzte 1892, p. 696.

\*) Maximum dose, according to Kobert, 0.004 gramme ( $\frac{1}{16}$  grain) and daily dose 0.008 gramme ( $\frac{1}{8}$  grain).

Klingenberg also gave digitalinum verum in alcoholic solution, although he was unable to detect any difference in its action whether given in solution or as pills. He prescribed a single dose of 0.002 gramme ( $\frac{1}{32}$  grain), and a daily dose of 0.01 to 0.015 gramme ( $\frac{1}{6}$ — $\frac{1}{4}$  grain), and later of 0.004 to 0.006 gramme ( $\frac{1}{16}$ — $\frac{1}{10}$  grain). His experiments are very instructive, for he compared the action of digitalinum verum with that of digitalis infusion in the same patient. But in spite of perfectly reliable experimental methods, his results were less favourable than were those of Pfaff. To quote his results:

"Digitalinum verum has the advantage over digitalis infusion of reliable dosage and the absence of all by-effects. — In the milder, compensated cases of valvular disease a certain influence on the pulse cannot be denied. — In all severe, uncompensated cases of valvular disease it is quite unable to replace the use of digitalis infusion."

From these communications no definite conclusion can be drawn as to the value of digitalinum verum.

**Digitalinum Purum Amorph.** Pharmacop. Belgic. II. (Digitaline chloroformique Pharmacopée Française 1884.)

The digitalin of the Pharmacopœa Belgica II, which was required to be completely soluble in chloroform and only with difficulty soluble in water, has of late been little used in therapeutics in consequence of the various special preparations of digitalis which have been issued in recent years. The following literature may be consulted for details regarding its pharmacological and clinical tests:

Lemaistre, Expériences sur la digitaline. Union médicale 1852, p. 212.

Leroux, Observation d'empoisonnement par les granules de digitaline. Union médicale 1852, p. 398.

Lange, Digitalin bei Lungentuberkulose, Herzkrankheiten, Wechselieber, Wassersucht und Albuminurie. Deutsche Klinik 1854, p. 141.

Siegmund, Einwirkung des Digitalins auf Nervus vagus und Harnstoffausscheidung Virchows Archiv Vol. 7, p. 238.

Christison, Über Digitalin. Günzburgs Zeitschrift für klinische Medizin Vol. 6, No. 6.

Vulpian, De l'action de la digitaline sur les batraciens. Gazette médicale de Paris 1855, p. 559.

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Klingenberg, Archiv für experimentelle Pathologie 1894, Vol. 33, p. 353.

Lefort, Journal de pharmacie 1864, II, p. 103, 1867, II, p. 424.

Gourvat, Journal de pharmacie 1871, II, p. 386.

Bardet, Nouveaux remèdes 1890, p. 311.

Before the appearance of the last edition of the French pharmacopœia (1908) it was customary in France, when "digitaline" was prescribed, to dispense digitalinum purum amorph., now only digitoxin is official. (Compare Semaine médicale 1908, p. 433.)

Digitalinum purum amorph was chiefly given *per os* in the form of pills or granules. The single dose lies between 0.00025 and 0.0015 gramme ( $\frac{1}{250}$ — $\frac{1}{40}$  grain), the maximum daily dose is 0.002 gramme ( $\frac{1}{32}$  grain). (Compare Merck's Index 1910, p. 95.)

References to the literature of digitaline cristallisée (Nativelle):

Adrian, Semaine médicale 1892, p. 147. — Presse médicale 1897, p. LIII, CCXVI.

Bardet, Presse médicale 1897, p. CCXXIII.

Bottu, Presse médicale 1909, p. 8.

Crinon, Semaine médicale 1892, p. 169.

Franck, Semaine médicale 1895, p. 287, 383.

Heger, Semaine médicale 1892, p. 223.

Lépine, Semaine médicale 1892, p. 21.

Maurel, Presse médicale 1909, p. 319.

Potain, Semaine médicale 1892, p. XXXIV.

Rosenthal, Presse médicale 1902, p. 367.

Yvon, Semaine médicale 1892, p. 514.

### Digitaletin.

At the present day digitaletin always signifies "digitaletin Schmiedeberg", but it must not be forgotten, in studying the literature on the subject, that formerly digitaletins of Nativelle and of Buignet existed, and that with regard to these pharmacological and therapeutic communications have been published, which must not be applied to digitaletin Schmiedeberg.

A perfectly pure digitaletin has not as yet been issued, but I have recently succeeded in preparing a comparatively very pure preparation, which might be found very suitable for therapeutic purposes. Digitaletin has so far been represented in therapy by digalen, which, according to Kiliani, consists of a solution of digitaletin in water. Cloetta at first took it for a soluble digitoxin. I have referred to this in my last Annual Reports\*).

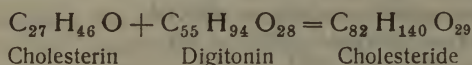
\*) Merck's Reports 1904—1909.

With regard to the pharmacological action of digitalein, this is, according to Schmiedeberg, identical with that of digitalin. Koppe also found that digitalein had the same action as digitalin and digitoxin, but in order to obtain its action considerably higher doses are necessary than is the case with digitoxin. According to Krailsheimer, 0.004 gramme ( $\frac{1}{16}$  grain) of digitalein corresponds to about 0.0003 gramme ( $\frac{1}{200}$  grain) of digitalin (Germanicum), and to 0.0001 gramme ( $\frac{1}{640}$  grain) of digitoxin, as regards pharmacological action.

### Digitonin.

As has been proved by Böhm, digitonin does not act on the heart. It has, therefore, not found any use in therapeutics. On the other hand it has recently proved of physiological and chemical interest, as Windaus has used it in order to carry out a comparatively simple quantitative estimation of cholesterin, which is physiologically of so much importance.

Windaus discovered that digitonin formed with cholesterin in alcoholic solution an additive product which was practically insoluble in alcohol, consisting of one molecule of digitonin and one molecule of cholesterin:



For the quantitative estimation of cholesterin, the material to be examined is dissolved in 50 times the amount of boiling alcohol 95 p.c. and a 1 p.c. solution of crystallised digitonin in hot alcohol 90 p.c. is added so long as a precipitate is formed. After allowing it to stand for several hours, the precipitate of the digitonin-cholesteride which has resulted is collected in a Gooch crucible, washed with alcohol and ether and dried at 100° C. By weighing this the amount of cholesterin can be calculated by multiplying the amount of cholesteride obtained by 0.25. As the cholesterin esters

Schmiedeberg, Archiv für experimentelle Pathologie 1875, Vol. 3, p. 33.

Koppe, ibidem 1875, Vol. 3, p. 274.

Krailsheimer, ibidem 1910, Vol. 62, p. 304.

Böhm, Archiv der Pharmazie 1892, Vol. 230, p. 260.

Windaus, Zeitschrift für physiologische Chemie 1910, Vol. 65, p. 110. Compare also Berichte der deutschen chemischen Gesellschaft, Berlin 1909, p. 238.

do not react with digitonin, the method described can also be utilised for the separation of cholesterin and cholesterin esters. The insolubility of digitonin cholesteride also enables it to be used as a qualitative test for cholesterin; but this reaction is not so delicate as the colour reactions usually employed for cholesterin.

The value and the utility of Windaus's method for the estimation of cholesterin as described above was experimentally confirmed by A. Lapworth. This author points out that after the precipitation of the cholesterin, the cholesterin esters can be hydrolised by caustic potash and then estimated by precipitating the digitonin.

There are a number of vegetable principles which in spite of their different derivation and in spite of somewhat wide differences in their general chemical properties possess a pharmacological action so analagous to that of the digitalis substances that they can without hesitation be united to form a definite pharmacological group. For this group Schmiedeberg has suggested the designation "digitalin group", and which has been generally adopted. Besides the digitalis substances proper described above, i. e., the substances obtained from *Digitalis purpurea*, the bodies to be described below, which are derived from other vegetable sources, belong to this digitalin group. In referring to these I shall in general restrict myself to those which are used therapeutically owing to their properties and actions being of pharmacological, physiological and clinical importance; while with regard to their chemical constants the reader should refer to the literature on the subject, in order that too much space may not be taken up here.

### Adonidin.

Several species of *Adonis* (belonging to the natural order Ranunculaceæ) have for a long time been considered of value as substitutes for digitalis leaves in heart disease\*), and

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Lapworth, Journal of Pathology Vol. 15. — Deutsche Medizinal-Zeitung 1911, p. 552.

\*) Compare P. Albertoni, On *Adonis aestivalis*. *Annali di chimica e di farmacologia* 1887, p. 198. — F. Borgiotti, Clinical Reports on *Adonis aestivalis*. *Annali di chimica e di farma-*

more especially since Bubnow carefully investigated both physiologically and clinically the leaves of *Adonis vernalis*. This author discovered the striking fact that the *Adonis* herb not only possesses the entire action of *digitalis*, but also has two invaluable properties, namely that it is free from cumulative action and that even when used for a period of many months no diminution of its therapeutic effects is observed. On account of these very favourable reports V. Cervello examined the leaves of *Adonis vernalis* and *Adonis cupana*, Y. Tahara and Y. Inoko the leaves of *Adonis amurensis*, and N. Kromer the leaves of *Adonis æstivalis* with reference to their active constituents.

Cervello, as a result of his researches, found a glucoside, which he called adonidin, the isolation of which from *Adonis vernalis* and *Adonis cupana* he described minutely. The pharmacological test of its action showed that it possessed the same action as *digitalis*, and on account of the absence of cumulative action already mentioned, adonidin promised to be of great utility in therapeutics. Tahara found in *Adonis amurensis*, which is cultivated as an ornamental plant in Japan, a glucoside the chemical formula of which was identical with that of the adonidin described by Cervello. But as, according to Inoko, its physiological action, although agreeing with that of adonidin qualitatively, was very much weaker quantitatively, the authors named it "adonin". The adonidin isolated by Kromer from *Adonis æstivalis*, according to Kobert, has an action about 200 times weaker than that prepared from *Adonis vernalis*, so that the glucoside is now only prepared from the last named plant.

The adonidin supplied by me, which is prepared from

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cologia 1888, p. 3. — P. Marfori, *Adonis æstivalis*. *Sperimentale* 1887, p. 357. — Mordagne, *Adonis vernalis*, Thèse de Paris 1885. — Durand, *Adonis* and *Adonidin*. *Bulletin général de thérapeutique* 1886, p. 63.

Bubnow, *Dissertation* Petersburg 1880. *Petersburger medizinische Wochenschrift* 1879, No. 1. — *Deutsches Archiv für klinische Medizin* 1883, Vol. 33, p. 262.

Cervello, *Archivio per le scienze mediche* 1881. *Archiv für experimentelle Pathologie* 1882, Vol. 15, p. 235. *Gazzetta chimica italiana* 1886, p. 493.

Tahara, *Berichte der deutschen chemischen Gesellschaft* 1891, Vol. 24, p. 2579.

Inoko, *Archiv für experimentelle Pathologie* 1891, Vol. 28, p. 302.

Kromer, *Archiv für Pharmazie* 1896, Vol. 234, p. 452.

*Adonis vernalis*, is a light brown, amorphous, hygroscopic powder, which easily cakes and is readily soluble in water and alcohol. It is indicated in valvular disease with disturbed compensation, angina pectoris, myocarditis, fatty heart, dropsy, parenchymatous nephritis with diminished diuresis, nicotine poisoning, and as an anæsthetic in ophthalmology. It is contra-indicated in high blood pressure, abnormally increased cardiac action, and in nervous heart trouble.

The following communications deserve special mention:

Desplats and Huchard report upon the excellent results obtained by them by the administration of adonidin in loss of compensation and in cardiac weakness. This drug was even found to be of use in cases in which digitalis and convallaria had proved useless. Huchard prefers adonidin to the galenical preparations of adonis, such as extract of adonis and tincture of adonis, and especially points out its utility in low blood pressure consequent upon adynamic fever (typhoid). In his experience it not only raises the blood pressure, but in heart disease it diminishes and eliminates arrhythmia, palpitation, œdema and dyspnœa, and often considerably increases diuresis. Huchard recommends as a daily dose 0.02 gramme ( $\frac{1}{3}$  grain) for after daily doses of 0.03 gramme ( $\frac{1}{2}$  grain) he observed vomiting and diarrhœa. As a single dose he was accustomed to give 0.005 gramme ( $\frac{1}{12}$  grain). Desplats also observed repeated vomiting in a patient, who by mistake had received 0.12 gramme (2 grains) a day. On the other hand, in his opinion, the preparation may be given more frequently in order to obtain a permanent result, as no cumulative action need be feared.

Oliveri made use of adonidin as a cardiac tonic and diuretic in cases of mitral and aortic insufficiency and was in every case able to alleviate the precordial pain, dyspnœa and palpitation. On account of the energetic action of adonidin, the author advises that the single dose should not exceed 0.06 gramme (1 grain) as a higher dose might cause vomiting, gastric trouble and nervous disturbances. For this reason it is given in chloroform water in 4 daily doses of 0.01 to 0.03 gramme ( $\frac{1}{6}$ — $\frac{1}{2}$  grain). Chloroform water offers the

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Desplats, communicated by Durand, *Bulletin général de thérapeutique* 1886, p. 63. Compare also Durand, *Thèse de Paris* 1885. Huchard, *Union médicale* 1886, p. 35 and 49. Oliveri, *Lancet* 1888, p. 24.

additional advantage that when adonidin is dissolved in this medium it keeps better than in an aqueous solution. As adonidin is very hygroscopic and easily cakes the best method for effecting its solution is to open the little glass tube containing the preparation and to drop it into the exact amount of water required for the solution. In this way the desired solution is obtained in the shortest time. (Compare Merck's Report 1894.)

According to H. Stern, adonidin is in many respects superior to digitalin or digitalis. It is said to be of special value in cases in which digitalis may only be used with the greatest care, e.g., fatty degeneration of the cardiac muscle, pericarditis, simple and compensatory hypertrophy and certain atheromatous conditions. The same holds good for renal disease. In rapidity and duration of action adonidin, according to Stern, is equal to nitroglycerin and is superior in this respect to all other cardiac tonics. The diuretic effect of the drug is best seen in dropsy and in lowered arterial tension. On the whole the author considers adonidin one of the most valuable cardiac tonics, which is always well borne when not given in too large doses. He made use of the following prescriptions:

Rp. Adonidin 0.01 gramme ( $\frac{1}{6}$  grain)

Sod. benz. 1.50 grammes (24 grains)

Ft. pulv. Mitte X.

Sig. One powder to be taken in a glass of water every 4 hours.

(In chronic nephritis.)

Rp. Adonidin 0.05 gramme ( $\frac{3}{4}$  grain)

Aq. destill. 10.0 grammes ( $\frac{1}{3}$  oz)

Sig. 1 to 2 c.c. (17—34 min.) to be injected subcutaneously.

(Angina pectoris, etc.)

Rp. Adonidin. 0.005 gramme ( $\frac{1}{12}$  grain)

Ammon. carbon. 0.1 gramme ( $\frac{1}{2}$  grains)

Camphor. 0.03 gramme ( $\frac{1}{2}$  grain)

Ft. pulv. Mitte XX.

Sig. One powder to be taken 3 times a day.

(In nicotine poisoning.)

The use of adonidin as a local anæsthetic in ophthalmology was suggested by A. Schidlowski, who considered its action to be effective in the treatment of various affections of the eye, such as acute and chronic glaucoma, iritis, iridocyclitis and corneal affections, even though it is not equal to that of cocaine. The author suggests the use of a 1 p.c. aqueous solution, of which 3 drops suffice to alleviate the unbearable pain of glaucoma, or to produce the necessary amount of insensibility for operative procedures, such as extraction of cataract or tattooing. Two drops of a 2 p.c. solution produce complete anæsthesia within 25 minutes, which lasts for 3 to 4 hours. The instillation causes a certain amount of irritation, which must be allowed to subside (about 1 hour) before commencing the operation.

With regard to the dosage by mouth, the following facts may be noted: the single dose ranges from 0.002 to 0.03 gramme ( $\frac{1}{32}$ — $\frac{1}{2}$  grain); 0.1 gramme ( $\frac{1}{2}$  grains) may be considered the maximum daily dose. Blumenthal suggests 0.06 gramme (1 grain) as the maximum single dose, while Kobert gives the maximum dose as 0.005 gramme ( $\frac{1}{12}$  grain) and pro die 0.03 gramme ( $\frac{1}{2}$  grain).

Finally the work of J. M. Fuckelmann may be referred to, in which he points out that the adonidin of commerce contains two glucosides which act as cardiac poisons, "adonidinic acid" and "neutral adonidin". The two substances have a similar action on the heart, but adonidinic acid also possesses a hæmolytic action, which is absent in neutral adonidin.

### Antiarin.

As early as 1684 C. Spielmann described an arrow poison used by the inhabitants of Celebes; later Kæmpfer, Rumphius and others\*) reported upon its origin and the plant from which it was obtained; at the present time it is generally agreed that the arrow poison used by the inhabitants of the Malay Peninsula and of the Sunda Islands is obtained from the

Schidlowski, Dissertation Petersburg 1907.

Blumenthal, Medizinische Klinik 1908, p. 161.

Kobert, Arzneiverordnungslehre, 3<sup>th</sup> Edit., p. 333.

Fuckelmann, Dissertation Rostock 1911. — Sitzungsberichte der naturforschenden Gesellschaft Rostock 1911, Vol. 3.

\*) Compare Archiv für experimentelle Pathologie 1901, Vol. 45, p. 317—321.

milk-juice of *Antiaris toxicaria* (Leschenault), of the natural order Moraceæ, the so-called Ipu tree. The most active ingredient of this arrow poison is the cardiac poison antiarin, but Wefers Bettink has obtained other toxic substances from it, i. e., strychnine, brucine and upaine. It is therefore probable that the natives use for the preparation of their arrow poison the ingredients of other plants besides the milk-juice of the ipu tree.

Kiliani carefully examined the milk-juice of antiaris trees, collected by the explorer Stevens in Malacca, and following the directions of de Vrij and Ludwig, prepared from it antiarin. Its glucosidal nature became apparent on treatment with alcoholic hydrochloric acid, when it was split up into antiarigenin and a sugar, antiarose. Antiarin dissolves in sulphuric acid containing iron oxide, yielding a yellow or yellowish-red solution. Kiliani has recently demonstrated that two antiarins are contained in the milk-juice of *Antiaris toxicaria*,  $\alpha$ -antiarin and  $\beta$ -antiarin. The two substances are said to be equally toxic.  $\alpha$ -antiarin forms tabular crystals melting at  $220^{\circ}$  to  $225^{\circ}$  C.,  $\beta$ -antiarin forms needle-shaped or columnar crystals, melting at  $206^{\circ}$  to  $207^{\circ}$  C. For  $\alpha$ -antiarin Kiliani suggests the formula  $C_{27}H_{42}O_{10} + 4H_2O$ , whereas in his opinion the formula  $C_{22}H_{30}O_8$  for  $\beta$ -antiarin still requires confirmation. Seligmann has also worked with a mixture of the two antiarins, as is apparent from his description of the crystalline form of his antiarin.

The first pharmacological experiments with antiarin were carried out by Mulder, but its action on the heart was first studied in detail by Kölliker and Sharpey, who discovered that it possessed a paralysing action on the heart and nervous system. Then followed the investigations of Alfermann,

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Wefers Bettink, Pharm. Weekblad 1903, Vol. 40, p. 395.

Kiliani, Archiv der Pharmazie 1896, Vol. 234, p. 438.

Kiliani, Berichte der deutschen chemischen Gesellschaft Berlin 1910, p. 3574.

Stevens, Veröffentlichungen aus dem Königl. Museum für Völkerkunde, Berlin, Vol. 2 and 3.

De Vrij-Ludwig, Sitzungsberichte der k. k. Akademie in Wien 1868, Vol. 57, p. 56.

Mulder, Journal für praktische Chemie 1838, Vol. 15, p. 419.

Kölliker, Verhandlungen der physikalisch-medizinischen Gesellschaft Würzburg 1857, Vol. 8.

Alfermann, Dissertation Marburg 1865.

Bezold and Hirt, Braidwood, Buchheim and Eisenmenger, Cushny, Dybkowsky and Pelikan, Hedbom, Kobert, Müller, Nasse, Neufeld, Rosenthal, von Schroff, Seligmann, Stockman, Straub, Valentin, Krailsheimer and Trendelenburg, from which it is evident that antiarin, in experiments on animals, exhibits the characteristic action of digitalis glucosides. Several of the authors even found that it possessed a quantitatively stronger action. According to the most recent investigations (by Krailsheimer) digitoxin, g-strophanthin and antiarin are said to have an approximately equal action. Therefore, in carrying out therapeutic experiments with antiarin, the doses used should be the same as those generally used of digitoxin.

Clinical observations relating to antiarin have not, as far as I know, been published. It may be mentioned that I do not prepare antiarin.

### Apocynum Substances.

The presence of a cardiac poison in the root of *Apocynum cannabinum* (Apocynaceæ), which is indigenous to North America and is much used for the treatment of dropsy, was

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Bezold-Hirt, Untersuchungen aus dem physiologischen Institut in Würzburg 1873.

Braidwood, Medizinisches Zentralblatt 1864, p. 641.

Buchheim-Eisenmenger, Eckhards Beiträge zur Anatomie und Physiologie Vol. 5, p. 98.

Cushny, Journal of experimental Medicine 1897, Vol. 2, p. 244.

Dybkowsky - Pelikan, Zeitschrift für wissenschaftliche Zoologie 1862, p. 279.

Hedbom, Archiv für experimentelle Pathologie 1901, Vol. 45, p. 317.

Kobert, Archiv für experimentelle Pathologie 1887, Vol. 22, p. 77.

Müller, Dissertation Bonn 1873.

Nasse, Dissertation Leipzig 1866.

Rosenthal, du Bois-Reymonds Archiv 1865, p. 601, 1866, p. 647.

Schroff, Strickers medizinische Jahrbücher (Vienna) 1874, p. 259.

Seligmann, Journal of Physiology 1903, Vol. 29, p. 39.

Stockman, Pharmaceutical Journal 1893, Vol. 52, p. 945.

Straub, Archiv für experimentelle Pathologie 1901, Vol. 45, p. 346.

Valentin, Archiv für die gesamte Physiologie 1868, p. 455, 1869 p. 518, 1871 p. 104. — Archiv für experimentelle Pathologie 1877, Vol. 6, p. 318.

Krailsheimer, Archiv für experimentelle Pathologie 1910, Vol. 62, p. 300.

Trendelenburg, Archiv für experimentelle Pathologie 1910, Vol. 61, p. 256.

already assumed by Husemann, who considered this to be the active principle of the drug. This assumption was confirmed by te Water's investigations of this drug, in which the author succeeded in isolating two substances from apocynum root, the resinous apocynin and the glucosidal apocynein.

Apocynin, according to te Water, even in very small doses, caused the frog's heart to stop beating in systole. Apocynein is said to closely resemble digitalein in its properties and its solubility.

The apocynin prepared by me from *Apocynum* forms white crystals soluble in alcohol. Finnemore has demonstrated that it is aceto-vanillon, melting at  $115^{\circ}$  C., which, according to Moore, has only a slight action on the blood pressure in animals.

It may be noted that von Oefele obtained from the shoots of *Apocynum venetum* an extract-like body possessing a pronounced digitalis action, to which he gave the name of apocynitein. Furthermore, Ch. W. Moore obtained from the rhizome of *Apocynum androsæmifolium* a glucoside of the composition  $C_{14}H_{18}O_3$ , melting at  $170^{\circ}$  to  $175^{\circ}$  C., which is said to represent the active principle of the drug. The author named it apocynamarin, because it has an intensely bitter taste. Finnemore pronounced cynotoxin, a dilacton of digitic acid (Kiliani), or of an isomeric acid of the latter, to be the active principle of the rhizome of *Apocynum cannabinum*. According to Moore, this is most probably identical with apocynamarin.

For therapeutic purposes only extractum apocyni cannabini liquidum deserves consideration. Its action, according to the pharmacological investigations of Dotschewski, is similar to that of strophanthin and affects the heart in the same

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Husemann, Archiv für experimentelle Pathologie 1876, Vol. 5, p. 245.

te Water (Communicated by Schmiedeberg), Archiv für experimentelle Pathologie 1883, Vol. 16, p. 161.

Finnemore, Journal of the Chemical Society 1908, Vol. XCIII. Transact. p. 1520. — Proceedings of the Chemical Society 1909, Vol. XXV, p. 77.

Oefele, Journal der Pharmazie von Elsass-Lothringen 1891, p. 325.

Moore, Journal of the Chemical Society 1909, Vol. XCV. Transact. p. 750.

Dotschewski, Russkij Wratsch 1895, p. 899.

way as the other members of the digitalin group. Woodhull; Duprey and Tyson emphasise the diuretic action of the drug, which is most evident in healthy kidneys. Provided the doses be not too large it causes no vomiting, a fact which is confirmed by other authors, viz., Pawinski, Riebold and Dmitrenko. Millard asserts that it acts as a bitter tonic on the stomach and is for this reason to be preferred to digitalis. But as with all digitalis substances, vomiting may occur with apocynum medication in the case of sensitive patients. In such cases smaller doses must be given at shorter intervals, or the drug must be taken after food.

In recent valvular disease, Millard treated the loss of compensation successfully with a combination of apocynum and strychnine. In aortic stenosis, in the author's experience, apocynum frequently saves life, and even in mitral stenosis it gives better results than digitalis. The author considers the preparation of special value on account of its beneficial effect in insomnia.

Dmitrenko, in the treatment of disturbances of compensation due to myocarditis and valvular disease, gave 7 to 10 drops of fluid extract of apocynum 3 times a day; Robin, as an adjunct to theobromine medication, gave 30 drops 3 times a day.

Kraemer and Fehsenfeld have also expressed themselves well satisfied with the prompt action of the fluid extract. They recommend it specially in chronic cardiac insufficiency with severe disturbances of compensation, when digitalis has failed. The result is said to be surprisingly good in many instances. The pulse becomes fuller, stronger and slower, diuresis is greatly increased and the general condition rapidly improves. Fluid extract of apocynum is

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Woodhull, *British Medical Journal* 1897, p. 714.

Duprey, *Lancet* 1905, II., p. 955.

Tyson, *American Journal of Medical Sciences* 1908, No. 1.

Pawinski, *Nouveaux remèdes* 1904, p. 121.

Riebold, *Münchener medizinische Wochenschrift* 1910, p. 1878.

Dmitrenko, *Journal des praticiens* 1904, 11<sup>th</sup> June. — *Revue de thérapeutique* 1904, p. 500.

Millard, *Medical and Surgical Reports* 1898, p. 93.

Robin, *Bulletin de la société de thérapeutique* 1904, 24<sup>th</sup> February.

Kraemer, *Münchener medizinische Wochenschrift* 1909, p. 2320. —

Merck's Reports 1909, p. 198.

Fehsenfeld, *Münchener medizinische Wochenschrift* 1911, p. 141.

also of use if digitalis loses its effect or if it is considered advisable to discontinue the administration of the latter for a time. The tincture may be used in place of the fluid extract. Petteruti and Somma have found doses of 60 to 90 drops serviceable. For a medium dose 10 to 15 drops of the fluid extract may be given 3 times a day.

### **Cactus Grandiflorus.**

About 20 years ago American doctors discovered in the flower stalks of *Cactus grandiflorus* (*Cereus grandiflorus* Mill.) an active cardiac tonic, which was soon widely used, because in the form of fluid extract or tincture it is non-toxic and has no cumulative action. Orlando Jones, Boinet and Boy-Teissier assert that *Cactus grandiflorus* strengthens the action of the heart and increases the circulation and is therefore also useful in asthenia.

Aulde considers cactus extract a good stimulant and regulator of the heart's action, which, on account of the absence of cumulative action, may be used in the various forms of functional disturbances of the heart. As I have already stated in my Annual Reports\*), the author used it in combination with various other drugs, e. g., with nux vomica and pancreatin in cardiac disturbance occasioned by dyspepsia, with Fowler's solution in anasarca, œdema of the lower limbs with or without valvular disease, with ergotin in endometritis, leucorrhœa, etc., if these were accompanied by palpitation, etc.

According to Engstad, *extractum cacti grandiflori liquidum* may be regarded as a specific in angina pectoris. He obtained the best results by giving it in doses of 15 drops 3 to 4 times a day. Tincture of cactus is also said to be useful. Its maximum dose, according to Watson Williams, is 2 grammes (34 min.), given every four hours. Hills and

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Petteruti-Somma, *Il Policlinico* 1894, p. 285.

Jones, *British Medical Journal* 1890, p. 70.

Boinet-Boy-Teissier, *Semaine médicale* 1891, p. 387.

Aulde, *Semaine médicale* 1891, p. CX. — *The Chemist and Druggist*, Vol. 39, p. 191.

\*) Merck's Reports 1891 and 1893.

Engstad, *Therapeutic Gazette* 1890, p. 606. — *Semaine médicale* 1891, p. II.

Williams, *Practitioner* 1891, p. 266.

Hills, *Therapeutic Gazette* 1891, p. 295.

Williams confirm the beneficial action of *Cactus grandiflorus*, especially in the milder cases of angina pectoris. But on the whole they do not consider that the drug can totally replace digitalis. They recommend its use in functional cardiac conditions, after sexual excess, and for the after-effects of over-indulgence in tobacco and alcohol, in Graves' disease and aortic insufficiency. But in mitral insufficiency and dilatation of the heart it is said to act less well than digitalis or strophanthus.

Zelenski recommended the fluid extract for delayed absorption of pleural exudates and for cardiac weakness. In his experience it is also indicated in badly compensated aortic valve lesions, as it is a safe drug in the treatment of oedema, dyspnoea and arrhythmia. It is said to act less well in badly compensated mitral valve lesions. According to Zelenski, in order to obtain a satisfactory action at least 30 drops should be given 3 times a day.

If the employment of *Cactus* preparations is occasionally followed by failure, as reported by Hatcher and Bailey, the explanation is certain to be found in the use of a deteriorated or substituted drug. According to Holmes, the inactive stems of *Opuntia decumana* have in fact been substituted for the true drug. Sharp also has reported on true and false *Cactus grandiflorus*. Curtin also considers failures in the use of *Cactus grandiflorus* to be due to the employment of substituted drugs, and therefore suggests a careful test of the drug. He considers *Cactus grandiflorus*, when correctly used, to be one of the most excellent cardiac tonics even though it cannot wholly replace digitalis in every case, and especially not in advanced cardiac weakness. It acts, however, as an excellent cardiac tonic in less severe weakness and in cardiac irritability, and is useful as an adjunct to other cardiac tonics. The author recommends it especially in cardiac debility following infective diseases, in Graves' disease, in and after influenza, in cardiac asthma, and com-

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Zelenski, *Klinisch-therapeutische Wochenschrift* 1902, p. 738.

Hatcher-Bailey, *Journal of the American Medical Association* 1911, 7<sup>th</sup> January.

Holmes, *Pharmaceutical Journal* 1897, p. 165.

Sharp, *Pharmaceutical Journal* 1897, p. 539.

Curtin, *Therapeutic Gazette* 1908, 15<sup>th</sup> November. — *Revue de thérapeutique* 1909, p. 22.

bined with nitroglycerin for older people suffering from cardiac debility, dyspnoea and asthma. It is also useful as a tonic in increased excitability of the heart consequent upon aneurysms, when digitalis is not indicated. The harmless fluid extract or the tincture may be given in doses of 5 to 30 drops several times a day\*).

On examining *Cactus grandiflorus* Teissier found an alkaloid which he named cactine, to which the therapeutic action of the drug is attributed\*\*). Farr confirmed the presence of small quantities of alkaloid in this plant, while Sharp and Hoseason detected neither an alkaloid nor a glucoside, but were able to confirm the diuretic action of *Cactus grandiflorus*. The preparation named "cactine" or "cactina" supplied by a foreign firm has, according to Hatcher's investigations, practically no action on the heart.

### **Carpaine.**

In 1889 M. Greshoff found an alkaloid, which he named carpaine, in the leaves of *Carica Papaya*, of the natural order Caricaceæ, indigenous to South America and cultivated in India. It forms white crystals, melting at 119° to 120° C., soluble in alcohol, ether, chloroform, and amyl alcohol. Its hydrochloride,  $C_{14}H_{25}NO_2 \cdot HCl$ , is soluble in water. Carpaine and its derivatives have been examined chemically by J. L. van Rijn and by Litterscheid, pharmacologically by Greshoff and C. L. Rümke, therapeutically by von Oefe.

\*) Compare Gregory, Therapeutic Gazette 1891, p. 426.

Teissier, Bulletin de thérapeutique 1891, p. 343.

\*\*) Compare Myers, New York Medical Journal 1891, 13th June.

Farr, Jahresberichte der Pharmazie 1898, p. 95.

Sharp-Hoseason, Pharmaceutical Journal 1894, p. 416.

Hatcher, Journal of the American Medical Association 1907, p. 1021.

Greshoff, Mededeelingen nit's Lands Plantenteien te Batavia 1890, Vol. 7. — Merck's Reports 1891.

van Rijn, Dissertation Marburg 1892. — Archiv der Pharmazie 1893, Vol. 231, p. 184 and 1897, Vol. 235, p. 332. — Nederlandsch Tijdschrift voor Pharmacie Vol. 5, p. 131 and Vol. 9, p. 47.

Litterscheid, Archiv der Pharmazie 1900, Vol. 238, p. 230.

Rümke, Nederlandsch Tijdschrift voor Pharmacie 1893, No. 3.

von Oefe, American Medical and Surgical Bulletin 1893, p. 1050.

Merck's Reports 1891.

After Greshoff had shown carpine to be relatively slightly toxic, the lethal dose for a hen weighing 500 grammes being 0.2 gramme, von Oefele carried out several tests with it. According to his results, the alkaloid causes no local irritation when injected subcutaneously, and the internal administration of 0.025 gramme ( $\frac{2}{5}$  grain) pro die exhibits no advantages over the well known digitalis substances. On the other hand, the subcutaneous injection of 0.006 to 0.01 gramme ( $\frac{1}{10}$ — $\frac{1}{6}$  grain), a dose which may be repeated daily or every second day, produces within a few minutes a beneficial action on the heart; in aortic stenosis and insufficiency the pulse rate is lowered, respiration is relieved and diuresis is considerably increased. Rümke admits that carpine is a cardiac poison, but his investigations show that its action does not correspond with that of digitalis, for it has a paralysing action only on the muscles and does not affect the nerves. It should therefore, like sparteine, be placed in the class of cardiostatics, and not, like digitalin, in that of the cardiac tonics.

### Cerberid.

In 1864 de Vrij described a glucoside which he had obtained from the seeds of *Cerbera Odallam* Gärt. (Apocynaceæ). This preparation, called by the author "cerberin", was examined together with other substances in a comprehensive work by Plugge; from the latter it was apparent that the cerberin of Vrij was neither identical with the thanginin prepared from *Cerbera Thanginia* Hook, nor with the thevetin prepared from *Thevetia Yccotli* D. C. (*Cerbera Thevetia* L.). Neither is the cerberin described by me in 1892 identical with Vrij's preparation. In order to prevent confusion, I have given the name of "cerberid" to the glucoside prepared by me from the seeds of *Thevetia Yccotli*.

Cerberid,  $C_{25}H_{38}O_{12}$ , is an amorphous, yellowish powder, soluble in water. Its chemical properties are not similar to those of thevetosin, isolated by Herrera from *Thevetia Yccotli*. On hydrolysis it splits up into glucose and cerberiresin.

According to the pharmacological tests carried out by Zotos with cerberid, this glucoside possesses the cardiac

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de Vrij, Sitzungsberichte der Wiener Akademie, 14<sup>th</sup> January 1864.

Plugge, Archiv der Pharmazie 1893, p. 10.

\*) Merck's Reports 1892.

Zotos, Dissertation Dorpat 1892.

action characteristic of substances belonging to the digitalin group. But, in contradistinction to digitoxin and thevetin, its subcutaneous injection rarely causes local irritation, and when instilled into the conjunctiva it causes no inflammation. Wagner, on the other hand, observed unpleasant symptoms of irritation of the subcutaneous tissue after the hypodermic injection of cerberid in doses of 0.0005 to 0.001 gramme ( $1/125$ — $1/64$  grain). Internally the author has given it in daily doses of 0.001 to 0.015 gramme ( $1/64$ — $1/4$  grain). The conclusions he draws from his clinical experiments are as follows: "Cerberid is a cardiac poison, which in man has an injurious effect on the intestinal tract and the stomach. The general weakness and feeling of exhaustion which follow the administration of the drug may be attributed to its action on the striped muscles. Cerberid has no action on the central nervous system. It displays only in a slight degree the regulating action of digitalis on the heart and this did not appear in all the patients on whom the drug was tested. In some it called forth a retardation, in others an acceleration of the cardiac rhythm, without exhibiting much effect upon respiration. The slight rise in blood pressure and the negligible increase in the amount of urine do not make up for its injurious action on the digestive organs." Although cerberid possesses so little therapeutic effect, it is strange that the author should state that he observed a strong cumulative action.

### Convallamarin.

The use of *Convallaria majalis* as a diuretic in dropsy and as a cardiac tonic is quite old, but the interest in its therapeutic use was freshly awakened at the end of the last century\*). Thus Sée and Bochefontaine carried out

Wagner, Russkij Wratsch 1892, p. 1033. — Merck's Reports 1893, p. 35.

\*) Compare:

Coze and Simon, Comparative experiments on the action of Digitalis and *Convallaria majalis*. Répertoire de pharmacie Vol. 12, p. 222. — Bulletin général de thérapeutique 1883, p. 489.

Desplats, The action of *Convallaria* on the heart and kidneys. Journal des sciences médicales de Lille Vol. 4, p. 731. — Archiv der Pharmazie 1883, Vol. 221, p. 52.

Roberts, *Convallaria* in mitral Insufficiency with Dropsy. Practitioner Vol. 32, p. 215.

pharmacological experiments with aqueous and alcoholic extracts of this plant and confirmed its cardiac action. In frogs and dogs the suitable employment of these extracts in large doses caused the heart to stop beating in systole; while small, non-lethal doses slowed the pulse, and brought about slower and deeper respiration and a rise in the blood pressure. The two authors confirmed its fairly considerable influence on diuresis. On the whole, therefore, the action of convallaria agrees with that of digitalis.

Walz was the first to occupy himself with the isolation of the active principles; he obtained two substances, convallarin and convallamarin, and described them in detail. Convallamarin is the only one of interest to us, for according to Marmé it possesses the cardiac action.

Convallamarin, a glucoside with the chemical formula  $C_{23}H_{44}O_{12}$ , is a yellowish, amorphous powder, soluble in water and in dilute alcohol. On hydrolysis it forms convallamaretin and glucose.

Marmé, who examined convallamarin Merck pharmacologically, attributes to it the cardiac action briefly described

Herschel, The action of *Convallaria majalis*. Lancet 1883, p. 724.

Filhoud-Lavergne, Etude physiologique et thérapeutique sur le *Convallaria majalis*. Thèse de Paris 1883.

Talamon, *Convallaria majalis*. Union médicale 1883, p. 796.

Durand, Comparative experiments on the action of digitalis, *Convallaria* and Adonidin. Dissertation Paris 1885.

Friedländer, Über *Convallaria majalis*. Dissertation Berlin 1885.

Reboul, The physiological action of *Convallaria majalis* on the heart. Dissertation Lyon 1885. Lyon médical 1884, p. 35.

Ferreira, Clinical observations to establish the therapeutic value of *Convallaria majalis*. Union médicale 1885, No. 173, p. 998.

Hurd, A substitute for Digitalis; the *Convallaria majalis*. Boston Medical and Surgical Journal 1883, p. 198. — Prevost, Pharmacologie du muguet. Révue médicale de la Suisse romande 1883, p. 378.

Bruen, *Convallaria majalis*. Therapeutic Gazette 1886, p. 20.

Taylor, Clinical Observations. New-York Medical Record 1883, p. 87 and 117.

Sée-Bochefontaine, Journal de thérapeutique 1882, No. 13. — Beckurts Jahresbericht 1881, p. 73.

Walz, Jahrbuch für praktische Pharmazie 1844, Vol. 7, p. 281 and Vol. 8, p. 78. — Neues Jahrbuch für Pharmazie 1856, Vol. 5, p. 1 and Vol. 10, p. 145.

Marmé, Göttinger Nachrichten 1867, p. 160.

above, as well as a marked diuretic action. The results reported by Kobert, Howard, Singer, Steller, Gottlieb and Magnus, Loewenthal and others agree with these findings. Steller found that convallamarin exhibits an action on the nervous system injurious to the reflex activity by diminishing the sensory response of the spinal cord; the injurious action also involves the motor nerves. It is said to have no action on the peripheral nerves.

Maragliano and Lourie observed in their clinical experiments that after the administration of 0.25 to 1.0 gramme (4—15 grains) of convallamarin the arterial pressure was often considerably raised, the pulse rate and respiratory frequency were usually lowered, but were sometimes not influenced at all. If the preparation is given for a prolonged period, the experience of the authors is that a considerable increase in diuresis ensues without any unpleasant consequences. Diarrhœa, however, occasionally occurs, and this is also admitted by other authors. Convallamarin is most useful in valvular lesions with insufficient cardiac action. Maragliano has used it without benefit in pleuritic effusion.

Leubuscher used convallamarin in healthy and in diseased persons, but his results were negative, although the preparation used by him in experiments on animals showed a powerful cardiac action. Even with medium and with lethal doses he was unable to confirm its action of increasing the blood pressure. This contradictory result might be attributed to the source of the convallamarin employed. This is not to be wondered at when one considers that similar negative results have occasionally been obtained with all preparations belonging to the digitalis group, and further that the locality from which the plant has been collected and the drying of the drug, as well as variations in the preparation

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Kobert, Archiv für experimentelle Pathologie Vol. 22, p. 77.

Steller, On the Physiological Action of Convallamarin on the Nervous System. Therapeutic Gazette 1886, I, p. 9.

Gottlieb and Magnus, Archiv für experimentelle Pathologie Vol. 47, p. 135.

Loewenthal, Dissertation Würzburg 1885.

Maragliano-Lourie, Zentralblatt für die medizinischen Wissenschaften 1883, p. 769.

Leubuscher, Zeitschrift für klinische Medizin 1884, Vol. 7, p. 581.

— Deutsche Medizinalzeitung 1884, p. 60.

of the commercial product may easily lead to the production of weak or inactive preparations. The fact that the use of a good preparation leads to corresponding results has been recently proved by E. P. Noguera, who prescribed convallamarin with the most satisfactory results in several cases of mitral insufficiency with loss of compensation and in cardiac dilatation in typhoid fever, as well as in cardiac hypertrophy with feeling of oppression and dyspnoea. It should be noted that the drug must be discontinued if after 4 days no definite action on the pulse is observed. For adults Noguera prescribes 0.05 to 0.2 gramme ( $\frac{3}{4}$ —3 grains) a day, for children 0.02 to 0.04 gramme ( $\frac{1}{3}$ — $\frac{2}{3}$  grain) by mouth, in mixtures or pills. Adults may also be given 0.03 gramme ( $\frac{1}{2}$  grain) subcutaneously twice a day. The author considers the drug to be contra-indicated in advanced degeneration of the heart muscle, and in the presence of renal or hepatic disease.

Further experiments with convallamarin would seem to promise success, especially in cardiac lesions with œdema. Internally 0.05 to 0.06 gramme ( $\frac{3}{4}$ —1 grain) may be given every 2 hours; 1 gramme (15 grains) a day is usually considered the maximum dose\*). Subcutaneously several applications of 0.005 to 0.02 gramme ( $\frac{1}{12}$ — $\frac{1}{3}$  grain) might be given daily.

### Coronilline.

*Coronilla varia* and *Coronilla scorpioides* (Papilionaceæ) had long been in use as popular remedies for dropsy, pulmonary tuberculosis, febrile symptoms, and the sting of scorpions, when Cardot in 1886 drew attention to these drugs as cardiac tonics. According to Poulet, *Coronilla varia*, used in the form of (20 p. c.) tincture, or dried and used as a powder has proved of use as a rapidly acting means of alleviating paroxysmal tachycardia and for the pains of aortic stenosis and mitral insuffi-

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Noguera, Gaceta medica Catalana 1909, 31<sup>st</sup> October.

\*) Compare Kobert, Beckurts Jahresberichte 1886, p. 418. — Blumenthal, Medizinische Klinik 1908, p. 161.

Poulet, Bulletin de la société de thérapeutique 1891, p. 481. — Nouveaux remèdes 1891, p. 476. Compare also Delektorsky, Archives internationales de pharmacodynamie 1896, No. 1 and 2. — Pharmazeutische Zeitschrift für Rußland 1894, p. 455.

ciency. It is also of use in asystole as a continuation of, and a substitute for, digitalis medication. The tincture is given in single doses of 10 to 20 drops and in daily doses of 30 to 60 drops, the fluid extract 4 to 5 times a day in doses of 5 to 15 drops, or the powder in daily doses of 1 to 2 grammes (15—30 grains).

Poulet used the leaves of *Coronilla varia*, which in his experience taste less bitter than those of *Coronilla scorpioides*, and yet have the same action. But the leaves of coronilla, according to Kobert, excite vomiting and diarrhœa, so that it is better for therapeutic purposes to use the active principle of the plant, namely coronilline, which is prepared from the seeds of *Coronilla scorpioides*. It is a yellow powder, soluble in water and alcohol.

Coronilline was first tested pharmacologically by Schlagdenhauffen and Reeb, who found that the action of the glucoside was similar to that of digitalis, and when given to frogs in doses of 0.001 gramme it caused the heart to stop beating in systole. The authors place the toxic dose for a dog weighing 12 kilogrammes at 0.01 gramme, given subcutaneously, and 0.001 gramme, when given by intravenous injection. Prevost found that coronilline was practically identical in action with digitoxin, but Kakowski found that it differed from digitoxin in that it caused dilatation of the coronary arteries in warm-blooded animals, whereas digitoxin causes constriction of these arteries.

Spillmann and Haushalter sum up the results of their therapeutic investigations as follows:

“Coronilline may be looked upon as a cardiac tonic, which has a beneficial effect upon certain symptoms brought about by the insufficient energy of the cardiac muscle. — The beneficial effect becomes manifest soon after the drug has been taken, but disappears almost entirely if the administration of the drug be interrupted. — Its action gives rise to a stronger pulse, increased diuresis and decrease in œdema and

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Kobert, Intoxikationen 1906, II, p. 1212.

Schlagdenhauffen-Reeb, Journal de pharmacie d'Alsace-Lorraine 1884, p. 419 and 1888, p. 103, 1890, p. 3 and 1893, p. 144.

Prevost, Revue médicale de la Suisse romande 1896, p. 14.

Kakowski, Archives internationales de pharmacodynamie 1905, p. 21.

Spillmann-Haushalter, Revue médicale de l'Est 1889.

dyspnœa. — Coronilline, like digitalis, is inactive in advanced myocardial degeneration.”

Kobert regards the daily doses of 0.2 to 0.6 gramme (3—9 grains), mentioned in the literature, as toxic. Spillmann and Hauser recommended the following prescriptions:

Rp. Coronillin.	2.5 grammes (40 grains)
Pulv. Altheæ	0.5 gramme ( $7\frac{1}{2}$ grains)
Mucilag. Cydoniæ q. s. ut f. pil.	No. XXV
Sig. One pill to be taken 6 times daily.	

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Rp. Coronillin.	2.0 grammes (30 grains)
Tinct. Coronill. var.	20.0 grammes ( $\frac{2}{3}$ oz)
Glycerin.	5.0 grammes (60 min.)
Syrup. coffeæ	5.0 grammes (60 min.)
Sig. 10 drops to be taken 3 to 6 times a day.	

### Erythrophlœine.

Erythrophlœum Guineense Don. (Erythrophlœum judiciale Proct.), natural order Cæsalpiniaceæ, is one of the group of poisonous plants from which the natives of Central Africa prepare the poison for their arrows\*). Lewin was the first to point out that the arrow poison named by Christy Haya-poison, and derived from Harrar, contained pieces of the bark of erythrophlœum. The alkaloid erythrophlœine, prepared from the bark of Erythrophlœum Guineense, the so-called “Sassy bark”, by Gallois and Hardy and by me some 30 years ago, showed a digitalis-like action and also excited convulsions. Later, however, I succeeded in perfecting the preparation of erythrophlœine, so that the preparation I now supply, as Harnack has shown, causes no clonic convulsions (picrotoxin action), but possesses a pure digitalis action, causing a great rise in blood pressure. Glawatz came to the same conclusion. Lewin found that erythrophlœine (in 0.05—0.25 p.c. solution) possessed a considerable anæsthetic action and he

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\*) Compare also Lasnet, Pharmaceutical Journal 1900, Vol. 65, p. 2.

Lewin, Virchows Archiv Vol. 191, p. 575. — Berliner klinische Wochenschrift 1888, p. 61.

Gallois-Hardy, Archiv der Pharmazie 1879, p. 562.

Harnack, Archiv für experimentelle Pathologie 1882, Vol. 15, p. 403 and 1884, Vol. 18, p. 1.

Harnack, Berliner klinische Wochenschrift 1895, p. 759.

Glawatz, Dissertation Kiel 1891.

considered that it might replace cocaine in ophthalmic work. But other authors, for instance, Onodi and Liebreich, found that the alkaloid gave rise to severe local irritation of the cornea; Harnack confirmed this observation, using pure erythrophlœine.

According to Karewski, erythrophlœine has no action when applied externally or injected into inflamed tissue. But the author found it efficacious as an anæsthetic when applied to the nasal mucous membrane in a 5 p.c. aqueous solution for the extraction of polypi. He also claims to have carried out painlessly dental extractions, scraping of tuberculous granulations, and similar operations after an injection of 0.005 gramme ( $\frac{1}{12}$  grain). Guttman was also well satisfied with the action of erythrophlœine injections (of 0.0005 to 0.001 gramme ( $\frac{1}{125}$  to  $\frac{1}{64}$  grain) in 0.1 to 0.05 p.c. solution) in neuralgia, tuberculous dysphagia, syphilitic headaches, and spermatic cord neurroses following epididymitis. By employing these doses he observed freedom from pain, appearing after half an hour and lasting as long as eight hours.

Ramon Paus recently reported on the employment of erythrophlœine as a dental anæsthetic. He recommends the following combination:

Rp. Erythrophlœin. sulph.	1.0 gramme (15 grains)
Menthol.	1.0 gramme (15 grains)
Acid. carbolic.	4.0 grammes (60 grains)

In dental caries of the first and second degree a little cotton wool is moistened with it and applied to the sensitive spot, which is then covered over with cement and sandarac varnish. On the following day it can be opened up and drilled without causing pain. Before removing the pulp another application of the mixture is necessary. During the first few hours after its application a negligible amount of pain is felt. It is said to have the great advantage over arsenious acid of never causing pulpitis, periodontitis, alveolar necrosis or other unpleasant consequences. The tongue, however, should be protected from contact with the medicament, more especially if it is liable to injury by sharp teeth.

Onodi, *Medizinisches Zentralblatt* 1888, p. 225.

Liebreich, *Berliner klinische Wochenschrift* 1888, p. 161.

Paus, (communicated by M. Lindner), *Zahntechnische Rundschau* 1911, No. 16, p. 584.

The erythrophlœinæ sulphas prepared by me forms an amorphous, yellowish-white powder, soluble in water and alcohol. As a cardiac tonic the preparation deserves the special notice of clinicians, for on account of its solubility in water it can be used internally, subcutaneously, intravenously, and rectally. As it may be assumed that erythrophlœine has no cumulative action (Herrmann), those experiments would seem likely to succeed in which the alkaloid is used as a substitute for digitalis glucosides or digitalis infusion, on the appearance of cumulative symptoms when using the latter.

Clinical experiments have not as yet been carried out with the erythrophlœine which has the pure action of digitalis; and the experiments carried out by Herrmann with the erythrophlœine which was formerly prepared, and which also has an action similar to that of picrotoxin, cannot be applied to the present preparation. In diseases of the heart an internal dose of 0.002 to 0.004 gramme ( $\frac{1}{32}$ — $\frac{1}{16}$  grain) may be used (compare Merck's Index 1910, p. 101).

The anæsthetic action of erythrophlœine has been discussed by Koller, Schöler, P. Guttman, G. Gutmann, Hirschfeld, Karewski, Königstein, Reuss, Tweedy, Brandt, Lipp, Löwenhardt and Kaposi.

Koller and Schöler considered that the irritant symptoms of erythrophlœine, apparent in the occurrence of pain and slight cloudiness of the cornea, were not a consequence of caustic action, but were due, as in the case of cocaine, to disturbance of nutrition consequent upon paralysis of the nerves. Schöler considers the corneal cloudiness, which is observed on using more concentrated solutions and according

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Herrmann, *Medizinisches Zentralblatt* 1888, p. 973.

Koller, *Wiener medizinische Wochenschrift* 1888, p. 185.

Schöler, *Berliner klinische Wochenschrift* 1888, p. 202.

Guttman, *Berliner klinische Wochenschrift* 1888, p. 258.

Gutmann, *Berliner klinische Wochenschrift* 1888, p. 260.

Hirschfeld, *Berliner klinische Wochenschrift* 1888, p. 222.

Karewski, *Therapeutische Monatshefte* 1888, No. 4.

Königstein, *Therapeutische Monatshefte* 1888, No. 4.

Reuß, *Internationale klinische Rundschau* 1888, No. 9.

Tweedy, *Lancet* 1889, p. 249.

Brandt, *Therapeutische Monatshefte* 1888, No. 6.

Lipp, *Wiener klinische Wochenschrift* 1888, p. 353.

Löwenhardt, *Berliner klinische Wochenschrift* 1888, p. 189.

Kaposi, *Wiener medizinische Wochenschrift* 1888, p. 281.

to various authors may last from 12 hours to 14 days, of more serious import than the pain observed by Königstein, Tweedy and Reuss after the instillation of active solutions of erythrophlœine. According to Gutmann and Hirschfeld, the use of erythrophlœine does not cause loss of sensibility, but produces analgesia sufficient, for example, for the removal of foreign bodies from the eye. In order to avoid symptoms of irritation consequent on instillations into the eye and after subcutaneous injections, Guttmann and Karewski recommend the use of very dilute solutions. Kaposi also confirmed the appearance, after subcutaneous injections of erythrophlœine, of local symptoms of irritation, such as redness, swelling and pain, and when large doses are given, of other toxic symptoms, such as vertigo, dilated pupils, slowing of the pulse and of the cardiac action, and vomiting. His communication is of special interest in that it proves the use of the alkaloid to be free from great danger, for the symptoms of general intoxication described above only appeared on the injection of 0.02 gramme ( $\frac{1}{3}$  grain). Lipp even injected 0.03 gramme ( $\frac{1}{2}$  grain), but in several cases he observed slowing of the pulse, dyspnœa and palpitation after 0.01 gramme ( $\frac{1}{6}$  grain). These doses, however, offer little practical assistance in the therapy of heart disease, for it may be assumed that the authors mentioned above did not carry out their anæsthetising experiments on patients known to be suffering from heart disease. In such patients erythrophlœine would probably act differently than in persons having a healthy heart. In the treatment of patients suffering from heart disease, caution must be observed as regards dosage, which should begin with 0.001 to 0.002 gramme ( $\frac{1}{64}$ — $\frac{1}{32}$  grain), until the correct dosage has been definitely settled.

A body nearly related to erythrophlœine, at any rate chemically, is the alkaloid muawine, first prepared by me in 1890. Muawine hydrobromide is a yellowish, amorphous powder, soluble in water and alcohol. It is obtained from the bark of the so-called muawi tree, a native of Mozambique, and probably nearly related to *Erythrophlœum Guineense*. Sassy bark, as is generally assumed in the literature, is collected not only from *Erythrophlœum Guineense*, but also from related species, such as *Erythrophlœum Laboucherii* and *Erythrophlœum Coumingo*. But the origin of muawi bark has not been definitely settled. Muawine is certainly not identical with ery-

throphlœine, at least Kobert came to this conclusion after carrying out pharmacological experiments on cold-blooded and warm-blooded animals. It cannot be identical with the pure erythrophlœine prepared by me, because besides having an action similar to that of digitalis, it can give rise to clonic and tonic convulsions. Jacobsohn also found that muawine is more toxic than erythrophlœine.

### Helleborein.

Helleborein is a glucoside contained in the roots of *Helleborus niger* and *Helleborus viridis*, which was discovered by Marmé in 1864. Husemann and Marmé, and also Thaeter, have paid special attention to its preparation. The first-named authors gave it the chemical formula  $C_{36}H_{44}O_{15}$ , the last-named the formula  $C_{37}H_{56}O_{18}$ . When decomposed by means of hydrochloric acid, helleborein, according to Thaeter, splits up into helleboretin, glucose and acetic acid. The helleborein supplied by me is a yellowish powder, soluble in water and alcohol, insoluble in ether, which has a sweetish taste, and in the form of powder excites sneezing.

Both physiologically and pharmacologically helleborein is nearly related to the digitalis glucosides. It is a definite cardiac poison, which also has the cumulative action of digitalis. In small, frequently repeated doses it has a retarding influence on the action of the heart, in large doses an accelerating influence, and it always raises the blood pressure. The action of helleborein on respiration, diuresis and the nervous system is also similar to that of digitalis\*).

Kobert, Merck's Reports 1890.

Jacobsohn, Dissertation Dorpat 1892. — Merck's Reports 1892.

Marmé, Zeitschrift für rationelle Medizin (3) Vol. 26, p. 1.

Husemann-Marmé, Liebigs Annalen Vol. 135, p. 55.

Thaeter, Archiv der Pharmazie Vol. 235, p. 414.

\*) Compare Husemann, Die Pflanzenstoffe. 1882, p. 610.

van der Heide, Kumulative Wirkung des Helleboreins. Archiv für experimentelle Pathologie 1885, Vol. 19, p. 127.

Schütz, Einwirkung des Helleboreins auf die Magenbewegung. Archiv für experimentelle Pathologie 1886, p. 21 and 359.

Wybauw, Pharmakologische Wirkung des Helleboreins. Archiv für experimentelle Pathologie 1900, Vol. 44, p. 434.

Jacoby, Archiv für experimentelle Pathologie 1900, Vol. 44, p. 368.

Huldschinsky, Archiv für experimentelle Pathologie 1908, Vol. 58, p. 412.

For the further elucidation of the action of helleborein the result of a recent pharmacological investigation of the preparation by Wybauw may be quoted, who gives the following summary of his results:

I. The action of helleborein administered internally consists in:

- a) an increase in the pulse volume, with or without decrease in the pulse rate, and increase in the blood pressure and the work of the heart,
- b) following upon this a rapid decrease in the work, the blood pressure, the pulse volume and even of the pulse rate (this phase corresponds to peristalsis),
- c) the heart stops in systole.

These signs depend upon the following factors:

- a) Immediately upon the entrance of the poison into the ventricle, it causes irritation of the nervous mechanism which regulates the movements of the heart, an increased systole and a consequent longer diastole,
- b) a molecular alteration of the heart muscle, which has been minutely described by Schmiedeberg,
- c) finally irritation of the restraining apparatus, which brings about the cessation of the action of the heart; possibly this irritation depends upon the altered equilibrium of the muscle.

II. The action of helleborein applied externally depends upon:

- a) Irritation of the inhibitory centres,
- b) a very slow change in the musculature, which gradually restores to the ventricle the appearance of systole.

Thus helleborein in every case acts upon the musculature, the elasticity of which is increased, and upon all the nerve elements of the heart, either stimulating or inhibiting their action.

As a substitute for digitalis helleborein may be given internally in doses of 0.01 to 0.02 gramme ( $\frac{1}{6}$ — $\frac{1}{3}$  grain)

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Trendelenburg, Wirkungsmechanismus und Wirkungsintensität des Helleboreins. — Archiv für experimentelle Pathologie 1909, Vol. 61, p. 262.

Baldoni, Wirkungen des Helleboreins bei der Applikation auf die Herzoberfläche. Archiv für experimentelle Pathologie 1905, Vol. 52, p. 216.

several times a day\*). Van der Heide considers it advisable to use the preparation at relatively long intervals (of 24 hours) and in small doses, rather than at short intervals or in large doses. But in his opinion the appearance of cumulative symptoms need not give rise to alarm on account of threatened poisoning, even if digitalis or helleborein has been administered for some time; for, according to his experiments, the symptoms disappeared even if the administration of helleborein were continued. But, if during the first few days of the administration of helleborein no definite alteration in the cardiac action is observed, care is necessary, for the continuation of the drug in such a case might jeopardise the patient's life.

After the subcutaneous injection of helleborein only very slight local symptoms of irritation have been observed, especially if very dilute aqueous solutions of the drug were used. On account of the lack of clinical evidence, however, no exact dosage can be given.

It may be noted that helleborein has been suggested as a local anæsthetic, for, when instilled into the conjunctival sac of frogs, it is said to cause complete anæsthesia of the cornea in about 5 minutes. Venturini and Gasparini have used the glucoside in the place of cocaine in ophthalmic practice, and state that it has occasionally produced better results than cocaine. For operative procedures it is said to be of great value. 0.0015 to 0.002 gramme ( $\frac{1}{40}$ — $\frac{1}{32}$  grain) is said to anæsthetise the cornea and the conjunctiva of animals for 30 minutes, without causing irritation.

### Nerium Oleander.

In the bark and leaves of *Nerium Oleander* (Apocynaceæ) several glucosides are present, which were first isolated and described by Schmiedeberg. In spite of their digitalis-like action they have not been introduced into therapeutics, and for this reason these preparations cannot be

\*) Maximum doses: single dose 0.03 gramme ( $\frac{1}{2}$  grain), daily dose 0.12 gramme (2 grains). Compare Pharmazeutische Zentrallhalle 1889, p. 397 and Beckurts Jahresbericht 1886, Vol. 21, p. 418.

Venturini-Gasparini, *Annali di chimica e di farmacologia* 1888, p. 159. — *Nouveaux remèdes* 1888, p. 223.

Schmiedeberg, *Archiv für experimentelle Pathologie* 1883, Vol. 16, p. 149.

obtained in the market. For the sake of completeness they will be briefly described here.

Schmiedeberg describes neriin as a yellow, amorphous substance having a bitter taste and a neutral reaction; it is readily soluble in alcohol and water. The author was not certain whether neriin was identical with digitalein, but its properties make this seem probable, wherefore he named it "oleander-digitalein".

Neriantin is amorphous or crystalline according to its method of preparation. It has only a feeble action, similar to that of saponin or digitonin, and does not cause the frog's heart to stop beating in systole. On hydrolysis it splits up into sugar and neriantogenin.

Oleandrin is a colourless, amorphous substance, which turns yellow on keeping. It is soluble in alcohol and chloroform, but only slightly soluble in water. Pharmacologically it has the action of digitalis and a dose of about 0.00025 gramme ( $\frac{1}{250}$  grain) causes the frog's heart to stop beating in systole.

As Schmiedeberg had only been able to obtain a very small quantity of glucoside from the leaves of oleander, Pieszczyk examined the bark of this tree and found, besides the neriin described by Schmiedeberg, a crystalline, colourless glucoside, soluble in alcohol, melting at  $171^{\circ}\text{C.}$ , which he named rosaginin. According to the physiological tests carried out by Ehrenthal it is highly poisonous. In frogs it produces convulsive symptoms and causes the heart to stop beating in diastole. Besides this it is a powerful local anæsthetic. It may also be noted that Dubigadoux and Durieu, and likewise Leulier, claim to have found strophanthin in the bark of the Algerian oleander.

The glucosides neriodorin and neriodorein, isolated by Greenish from the seeds of *Nerium odoratum*, also belong

Pieszczyk, Archiv der Pharmacie 1890, p. 352. (In the two treatises of Schmiedeberg and Pieszczyk will be found all the older references relating to oleander, its active principles, and its therapeutic use.)

Ehrenthal, Archiv der Pharmazie 1890, p. 357.

Dubigadoux-Durieu, Journal de pharmacie et de chimie 1898, II, p. 433.

Leulier, Journal de pharmacie et de chimie 1911, II, p. 157.

Greenish, Pharmaceutical Journal 1880/81, p. 565 and 873 and 1883/84, p. 289. — Pharmazeutische Zeitschrift für Rußland 1881, p. 80. — Chemisches Zentralblatt 1881, p. 218.

to the group of cardiac poisons; but they have found no more favour in therapeutics than have the glucosides of oleander mentioned above.

Von Oefele recommends the tincture prepared from the fresh leaves of the Italian Nerium Oleander for therapeutic use, especially as a temporary substitute for digitalis medication. As a result of its internal use the pulse becomes slower, regular and strong, diuresis is almost always considerably increased, or if this is not the case, the specific gravity of the urine is increased. In practice the following prescription is used:

Rp. Tinct. nerii oleandri 10.0 grammes ( $\frac{1}{3}$  oz)

Aq. menth. pip. 1.0 gramme (17 min.)

Sig. 20 drops to be taken in sugar and water 3 times a day.

According to the author, the action of oleander resembles that of digitalis and also that of adonis and strophanthus, in that small doses only act after a time and large doses have a lasting action. The prolonged use of oleander tincture may give rise to dizziness and may disturb the appetite, by-effects of little moment when compared with those occurring as a result of digitalis medication.

**Ouabain cryst.** is identical with Gratus-strophanthin (strophanthin cryst.), which see.

### **Ouabain, amorphous.**

Amorphous ouabain\*) is prepared by me from the wood of *Acocanthera* (Schimperii or Deflersii), of the natural order Apocynaceæ, indigenous to East Africa. It forms an amorphous, white or yellowish powder, readily soluble in water. The following reports have reference to this preparation.

According to Lewin, ouabain, like erythrophloeine, causes deep anæsthesia of the mucous membranes. When administered subcutaneously or internally it has a toxic effect on

Oefele, Reichsmedizinalanzeiger 1891, p. 203. — Merck's Reports 1891.

\*) Compare Holmes, Pharmaceutical Journal 1893, p. 41. — Lewin, Archiv für pathologische Anatomie und Physiologie 1893, Vol. 134, No. 2. — Berliner klinische Wochenschrift 1906, p. 1583. — Merck's Reports 1893, p. 71; 1895, p. 100, 1906, p. 19. — Brieger, Archives internationales de pharmacodynamie 1903, p. 399. — Berliner klinische Wochenschrift 1903, p. 357. — Merck's Reports 1905, p. 1.

both cold-blooded and warm-blooded animals. In the latter death is accompanied by severe dyspnœa with clonic convulsions; dyspnœa and death are due to disturbances in the exchange of gases in the lungs, caused by disturbed cardiac action. Lewin, as early as 1893, suggested the possibility of its medicinal use.

It was not until 1906 that Stadelmann reported upon the substitution of an infusum ligni aëocantheræ for infusion of digitalis and offered clinical proofs of the utility of this drug. The author's earliest experiments with the glucoside ouabaïn were most promising. Its action was not only comparable to that of digitalin, but was superior to it in that subcutaneous and intramuscular injections of its solution were neither painful, nor did they cause inflammatory symptoms of any consequence. In more recent communications Stadelmann reports that an intramuscular injection of a 0.03 to 0.04 p. c. ouabaïn solution is only slightly painful. Sensitive patients complain only of a burning sensation, lasting 1 to 2 hours, which can be successfully treated by compresses of aluminium acetate solution. Other patients scarcely notice any pain. Ouabaïn is also suitable for subcutaneous and intravenous injection. When used thus, according to the author, it is only slightly painful, incomparably less so than digalen, which can be injected subcutaneously and intramuscularly in the same concentration and the same dosage. After injections of ouabaïn he has hardly ever seen infiltrations or inflammation, which almost always occur after using digalen. Intravenously the drug can also be used like digalen. The author begins with small doses of ouabaïn in order to test the action of the preparation and thus to avoid effects such as occur after the intravenous injection of digitalis substances. According to his account, only one injection was given, and repeated, if necessary, at intervals of 3 to 4 days, or if larger doses were employed, after 1 to 4 weeks. The injection was scarcely ever repeated within less than a week, only at first, when small doses of 0.0008 to 0.001 gramme ( $\frac{1}{80}$ — $\frac{1}{64}$  grain) were used, a second injection was given after 3 to 4 days. Stadelmann has never known disadvantages to accrue from this medication, nevertheless for any but desperate

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Stadelmann, Berliner klinische Wochenschrift 1906, p. 1586. — Merck's Reports 1906, p. 20. — Medizinische Klinik 1909, p. 1350 and 1392.

cases he advises an interval of at least a week, especially if a dose of 0.001 to 0.002 gramme ( $\frac{1}{64}$ — $\frac{1}{32}$  grain) has been given. The concentration of the solution was 0.04 p.c., and of this 3 to 6 c.c. (50—100 min.), corresponding to 0.0012 to 0.0024 gramme ( $\frac{1}{50}$ — $\frac{1}{25}$  grain) of ouabain were injected. But for therapeutic use the author considers a dose of 0.001 to 0.002 gramme ( $\frac{1}{64}$ — $\frac{1}{32}$  grain) sufficient. After the injection of 6 to 7 c.c. (100—120 min.) he observed by-effects, such as anxiety, palpitation, dyspnoea with increase in the pulse rate and vomiting. The cases treated were: aortic insufficiency, in some cases combined with arterio-sclerosis or nephritis, vitium cordis complicatum, mitral lesions, chronic nephritis with weak heart, in some cases combined with arterio-sclerosis, cardiac weakness combined with arterio-sclerosis or myocardial degeneration and conditions of collapse. The results obtained in these different cardiac lesions varied; in some cases they were good, in some satisfactory, in some transient and in some negative, just as is occasionally the case with digitalis, digalen, diuretin, strophanthus, caffeine, etc. The detailed reports of the author relating to the action of his method of treatment on the pulse, diuresis, and the general condition cannot well be given in abstract and should be referred to in the original. Whether ouabain is superior to other cardiac tonics cannot be determined from the statements which the author has given in an objective form, but it certainly deserves consideration from a medical standpoint. The author found that in those cases in which the preparation failed, other drugs such as digitalis and digalen were not usually more successful. Occasionally diuretin, theocin or strophanthus were of more use and sometimes these also failed; occasionally ouabain proved successful after the other drugs had failed.

From Stadelmann's most recent publication it appears that ouabain is likely to prove a most useful remedy which can be strongly recommended for general trial and use.

For internal administration Stadelmann prescribes the following solution:

Rp. Ouabain	0.004 gramme ( $\frac{1}{16}$ grain)
Aq. destill.	100.0 grammes ( $3\frac{1}{3}$ oz)
Aq. menth.	30.0 grammes (1 oz)
Syrup. ad	150.0 grammes (5 oz)

Sig. One tablespoonful to be taken every 2 hours.

This solution is said to have a bitter taste, but not as unpleasant as that of strophanthin. Four bottles of this solution were given, so that the patients took about 0.0004 gramme ( $\frac{1}{160}$  grain) for a dose, and 0.0024 gramme ( $\frac{1}{25}$  grain) in the course of a day; thus during the week of treatment they would take 0.016 gramme ( $\frac{1}{4}$  grain). The author did not obtain better results by means of this medication than by using digitalis or strophanthus; this he attributes to the severity of his cases and the employment of too small doses. He considers that double this dose may be given in the beginning and advises that as a test, mixtures should be prescribed containing 0.008 to 0.01 gramme ( $\frac{1}{8}$ — $\frac{1}{6}$  grain) of ouabain in 150 grammes (5 oz). In isolated cases the author has actually achieved satisfactory results with larger doses. Nevertheless intravenous and intramuscular injections are apparently more advantageous than internal administration. The intramuscular application gives the same results as the intravenous injection and is preferable to the use of other digitalis preparations which cause pain when applied in this way. In those cases in which internal digitalis medication is not well borne, intramuscular injections of ouabain should fill a considerable gap in the therapy of severe heart disease and the symptoms to which it gives rise. For intramuscular injection an aqueous solution of ouabain 0.004:10.0 ( $\frac{1}{16}$  grain in  $\frac{1}{3}$  oz) is used. According to the author, 1 c.c. (17 min.) of this is injected 3 to 4 times a day. The results in aortic insufficiency, mitral lesions, vitium cordis complicatum, myocarditis, nephritis, arterio-sclerosis with weak heart, oedema, etc., are said to be the same as those obtained by intravenous injection, which have been described above.

### Oxysparteine.

This base, first prepared by Ahrens by the oxidation of sparteine, forms white crystals, which turn yellow on keeping, and have the composition  $C_{15}H_{24}N_2O$ ; they melt at  $84^{\circ}C.$ , and dissolve in water, alcohol, ether and chloroform. The hydrochloride ( $C_{15}H_{24}N_2O \cdot HCl + 4H_2O$ ) serves for therapeutic use; it is soluble in water and alcohol.

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Ahrens, Berichte der deutschen chemischen Gesellschaft Berlin 1891, p. 1095.

In the pharmacological investigation of oxysparteine Hürthle found that the alkaloid has an action on the circulation of both cold-blooded and warm-blooded animals, which manifests itself in an increase in the cardiac activity. The capacity of the heart for work is said to be increased in most cases, without alteration in the vascular tone and in spite of the diminution in pulse rate.

According to von Oefele's communications, oxysparteine hydrochloride may be used therapeutically in cardiac lesions in which the tissue processes have not completely ceased, especially when accompanied by degenerative diseases of the myocardium. At the beginning the drug is given subcutaneously in doses of 0.04 gramme ( $\frac{2}{3}$  grain) and rapidly increased to 0.1 gramme ( $1\frac{1}{2}$  grains) as a dose, daily. Prolonged administration cannot be recommended as the organism soon becomes accustomed to the preparation. In the author's experience the simultaneous administration of opiates should be avoided, as oxysparteine then fails entirely.

Langlois and Maurange have found a new field of usefulness for oxysparteine. These investigators had previously found\*) that the subcutaneous injection of sparteine had a tonic and regulating effect on the cardiac action, should cardiac disturbances occur during chloroform anæsthesia. Oxysparteine has proved of still more use in this respect. According to the communications of the authors mentioned above, an injection of 0.03 to 0.04 gramme ( $\frac{1}{2}$ — $\frac{2}{3}$  grain) of oxysparteine hydrochloride and 0.01 gramme ( $\frac{1}{6}$  grain) of morphine hydrochloride is given about an hour before the operation, and thus anæsthesia is obtained which can be maintained by the use of very little chloroform. The heart-beat remains regular and strong, even if the respiration should become somewhat shallow. If the operation lasts longer than an hour, the injection of oxysparteine may be repeated after this time, but without the morphine. For this purpose the authors used a solution of 0.5 gramme ( $7\frac{1}{2}$  grains) of oxysparteine hydrochloride in 10 grammes ( $\frac{1}{3}$  oz) of aqua amygdalarum amar., of which they injected 6 to 8 divisions of a Pravaz syringe.

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Hürthle, Archiv für experimentelle Pathologie 1892, Vol. 30, p. 149.  
von Oefele, Merck's Reports 1892.

Langlois-Maurange, Nouveaux remèdes 1895, p. 400.

\*) Compare Nouveaux remèdes 1894, p. 344.

**Periplocin.**

E. L e h m a n n was the first to isolate this glucoside from the bark of *Periploca græca*, natural order *Asclepiadææ*, indigenous to the Mediterranean districts. He described it as a crystalline substance, having the formula  $C_{30}H_{48}O_{12}$ , which is said to split up on hydrolysis into periplogenin and glucose. I have not succeeded in obtaining a crystalline substance from this drug. The periplocin prepared by me is an amorphous, yellow powder, soluble in water and alcohol.

There is no doubt that periplocin represents the active principle of *Periploca græca*, and, according to the investigations of B u r s c h i n s k y, it possesses a specific cardiac action. The first trials on patients suffering from heart disease were made by L e w a s c h e w, who used the following solution for subcutaneous injection:

Rp. Periplocin.	0.01 gramme ( $\frac{1}{60}$ grain)
Sod. chlor.	0.06 gramme (1 grain)
Aq. destill.	10.0 grammes ( $\frac{1}{3}$ oz)

Sig. 0.5 to 1 c. c. (8—17 min.) to be injected.

As a maximum daily dose the author used 0.001 gramme ( $\frac{1}{64}$  grain). The injections were given daily, or at intervals of 2 to 3 days. An hour after the injection the pulse rate diminishes, the blood pressure rises, the heart sounds and the organic sounds become more distinct, and diuresis increases considerably in the course of a few days. But diuresis is only increased if congestion be present consequent upon cardiac lesions, and not in renal or hepatic disease. In using the maximum dose Lewaschew has occasionally observed nausea, vomiting and diarrhœa. These symptoms, which are well known to occur when digitalis is used, cannot interfere with the general employment of periplocin. However, it had also been observed that injections of periplocin occasioned local irritation and pain. For this reason Cholewa proposed to administer periplocin nasally; it acts as well when given thus and is less dangerous. As a medium daily dose the author suggests 0.0005 gramme ( $\frac{1}{125}$  grain). The best

Lehmann, *Archiv der Pharmazie* 1897, p. 157.

Burschinsky, *Russkij Wratsch* 1896, No. 29—35. — *Petersburger medizinische Wochenschrift* 1897, Supplement No. 9, p. 49. —

Merck's Reports 1897, p. 64 and p. 117.

Lewaschew, *Russkij Wratsch* 1898, No. 11.

Cholewa, *Therapeutische Monatshefte* 1904, p. 292.

method of giving the drug is in 0.01 p.c. aqueous solution (5 c.c. [85 min.] as a dose) by means of a suitable spray into the nose and respiratory tract. By this method and dosage Cholewa has never observed the occurrence of unpleasant by-effects or cumulative action. After one or two applications of periplocin, according to the author, the whole body is suffused by a feeling of warmth, the pulse becomes fuller and more rapid. If shortness of breath is present the lung becomes clear and the breathing easier, the blood pressure falls and diuresis is increased. Even after small doses arrhythmia and the slight attacks of pseudo-angina, from which neurasthenics often suffer, cease. The action lasts for 24 hours, or longer. Periplocin is especially indicated in those cases in which congestion occurs as a consequence of disparity between vascular resistance and cardiac strength, and leads to dyspnoea and asthma, conditions which are also favoured by vasomotor neurasthenia. It is also indicated in ischæmic atony of the intestines, membranous enteritis, arterio-sclerotic contracted kidney and stenocardia, in which it is preferable to other diuretics because it does not interfere with digestion. In diseases of the heart and vessels, also, in which a prolonged use of digitalis would probably be required, the medication recommended by Cholewa is suitable.

According to Silberberg's communications, the intravenous employment of periplocin seems hopeful. It has the same effect as the other cardiac tonics, viz., it regulates and accelerates cardiac action. Simultaneously with the increase in cardiac action, the blood pressure and diuresis are increased. The augmentation of cardiac action is especially apparent in cardiac lesions, the regulation of cardiac rhythm in myocarditis. The constant results of intravenous injections of periplocin are: increased rapidity of cardiac action and removal of the troublesome subjective sensations, such as attacks of stenocardia, shortness of breath and irregularity of the pulse; the action is immediate. But, according to Silberberg, the special advantage of periplocin over other cardiac tonics lies partly in the painlessness of the intravenous injections and partly in the absence of cumulative symptoms. Nor has the author ever seen other by-effects. According to Silberberg, the medium therapeutic dose is 0.001 gramme ( $\frac{1}{64}$  grain). The

sterilised periplocin solution of Lewaschew (compare above) might be used for this purpose in doses of 1 c.c. (17 min.).

### **Scilla Maritima.**

After the publication by Fagge and Stevenson of a communication to the effect that they had discovered a substance similar in action to digitalis in squills (*Urginea maritima* Barker = *Scilla maritima* L.), which has since olden times been used as a diuretic in dropsy, this drug was investigated by various observers with regard to its active principles\*).

As early as 1826 Tilloy described a bitter substance which he had obtained from *Scilla maritima* and which he called scillitin. According to Schroff, this was a substance having a narcotic and poisonous action, which was combined in the drug with a volatile acrid substance. Husemann, in contradistinction to Schroff, observed no cardiac action in experimenting with this preparation, and considered the contradictory results to be due to differences in the scillitin of commerce obtainable at that time. Mandet distinguished two substances, the poisonous sculein and the non-poisonous scillitin, the latter having a diuretic action. Jarmersted found a

Fagge-Stevenson, *Pharmaceutical Journal* 1865, Vol. 7, p. 421.

\*) Compare Boerhave, *Elementa chemiae*, Lipsiae. II, p. 122. — Cartheuser, *Rudimenta materiae medicae rationalis*, Frankfurt 1741, p. 244. — Trommsdorff, *Journal der Pharmazie* Vol. 1, p. 205. — Athanasius Trommsdorffs *Journal der Pharmazie* Vol. 3, p. 156. — Buchner, *Döbereiners Jahrbuch* 1811, p. 1. — Landerer, *Repertorium für Pharmazie* (1) Vol. 47, p. 442. — Righini, *Repertorium für Pharmazie* (2) Vol. 13, p. 87. — Vogel, *Annales de chimie* 1812, p. 147. — Lebourdais, *Annales de chimie* 1848, p. 62. — Bley, *Archiv der Pharmacie* 1850, Vol. 61, p. 141. — Marais, *Annuaire de thérapeutique* 1857, p. 94. — Thèse de Paris 1856. — *Journal de pharmacie* 1857, Vol. 31, p. 123. — Wittstein, *Buchners Repertorium für praktische Pharmazie* 1850, p. 189. — *Chem. Zentralblatt* 1850, I, p. 319.

Tilloy, *Journal de pharmacie et des sciences accessoires* 1826, Vol. 12, p. 635, 1853, Vol. 23, p. 406.

Schroff, *Zeitschrift der ärztlichen Gesellschaft in Wien* 1864, p. 43. Husemann, *Archiv für experimentelle Pathologie* 1876, Vol. 5, p. 254. — *Deutsche medizinische Wochenschrift* 1876.

Mandet, *Comptes rendus de l'académie des sciences* 1860, p. 87.

Jarmersted, *Archiv für experimentelle Pathologie* 1879, Vol. 11, p. 22.

glucoside in *Scilla maritima*, which is said to have been but slightly inferior to digitoxin in pharmacological action. This body, which he named *scillain*, was further investigated chemically by Kurtz, and pharmacologically by Kobert and Schütz. All these attempts to prepare from squills a uniform, active substance have not led to the desired result. I also have failed to isolate a substance of this description.

The *scillipicrin* supplied by me is a thoroughly purified extract, and the *scillitoxin* which I prepare is a resinous substance. Both preparations have been tested physiologically by Möller, and clinically by Frommüller, but they have not been introduced into therapeutics.

I issue *scillipicrin* in the form of yellow, or reddish-yellow, hygroscopic pieces. The preparation dissolves in water and is therefore specially suitable for subcutaneous injection. It has a definite action on the heart, which manifests itself in the retardation of cardiac action. In frogs, doses of 0.01 to 0.02 gramme cause the heart to stop beating in diastole. Therapeutically the drug is used in dropsy and in heart and kidney disease. A dose of 0.02 to 0.06 gramme ( $\frac{1}{3}$ —1 grain) in aqueous solution is injected subcutaneously once a day. According to Frommüller, *scillipicrin* is the preparation of *scilla* best suited for therapeutic use, as he considers it an excellent diuretic. He states that it is superior to all other diuretics. In 17 cases of severe oliguria reported by the author, he states that it only failed twice, while in all the remaining cases it doubled or trebled the amount of urine. In order to avoid symptoms of irritation, *scillipicrin* should not be injected in too concentrated a solution, for when a 10 p.c. solution was used Frommüller observed severe local irritation.

*Scillitoxin*, an amorphous, brownish substance soluble in alcohol, acts more energetically on the heart than does *scillipicrin*, and in sufficiently large doses causes the heart to stop beating in systole. It is used as a diuretic in nephri-

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Kurtz, Dissertation Erlangen 1894.

Kobert, Archiv für experimentelle Pathologie 1887, Vol. 22, p. 96.

Schütz, Archiv für experimentelle Pathologie 1886, Vol. 21, p. 360.

Möller, Dissertation Göttingen 1878.

Frommüller, Schmidt's Jahrbücher der gesamten Medizin, Vol.

186. — Memorabilien, Betz' Zeitschrift für praktische Aerzte (Heilbronn, Published by Scheuerlen) 1879.

tis and in cardiac lesions in doses of 0.001 to 0.002 gramme ( $\frac{1}{64}$ — $\frac{1}{32}$  grain) several times a day; 0.05 gramme ( $\frac{3}{4}$  grain) has been fixed as the maximum daily dose. Frommüller has frequently observed giddiness, headache and narcotic symptoms as by-effects produced by the preparation.

As the preparations of *Scilla maritima* mentioned above have not been sufficiently tested clinically, and make no pretence to chemical individuality and purity, we shall refer briefly to the use and therapeutic value of *Scilla maritima* itself and the galenical preparations made from it.

It is generally assumed that *Scilla maritima* and its galenical preparations, such as the tincture, the extract and the vinegar, have two kinds of action, a cardiac action, manifested by a rise in blood pressure, and in large doses by stoppage of the heart in systole, and secondly an action on the expectoration, the mechanism of which has not yet been satisfactorily explained. According to Husemann and König, the extract of scilla, in experiments on animals, acts on the heart and circulation in a similar manner to *digitalis*, i. e., in small doses it causes stronger and slower cardiac contractions. Apart from nausea and vomiting, symptoms which are well known to occur with all cardiac tonics, the authors noticed no unpleasant by-effects following the use of scilla medication. It can, therefore, be used in dropsy and whenever *digitalis* is indicated. It is usual to combine it with other diuretic drugs. The galenical preparations of squill in most general use are the extracts and the vinegar, which in the German Pharmacopœia are required to be prepared from the white variety of *Urginea maritima* Barker, although Schroff had pointed out that the red variety was more active. The preparation is given in single doses of 1 to 5 grammes (15—75 grains), and in daily doses of 30 grammes (1 oz). For the dosage of scilla extracts compare Merck's Index 1910, p. 115.

### Sparteine.

Broom (*Spartium scoparium* L., natural order Papilionaceæ) contains two pharmacologically active principles, sparteine and scoparin, of which sparteine, on account of its cardiac action, is the only one of interest to us at present. This alkaloid was first obtained from this plant by Stenhouse. Afterwards

König, Dissertation Göttingen 1875.

Stenhouse, Liebigs Annalen 1851, Vol. 78, p. 15.

Mills, Kirchmann, Houdé, Soldaini, Kley, Willstaetter and Marx, and others, reported on its preparations and tests.

For therapeutic purposes the sulphate ( $C_{15}H_{26}N_2 \cdot H_2SO_4 + 5H_2O$ ), a salt readily soluble in water and alcohol, is the most suitable.

According to the physiological and pharmacological investigations of Laborde, Légris, Germain-Sée, J. Fick, Harnack and Meyer, Dreser, Meyer, Cushny and Matthews, Muto and Ishizaka, Mitchell, de Rymon, Masius, Langgaard, Kauenhowen, Thomas, Garand, Griffé, Dontas, Gluzinski, Barton, and others, sparteine has an action on the heart which according to some is similar to or identical with the action of digitalis, while, according to others, it differs from the latter in that it does not, like digitalis, prolong systole, but prolongs diastole and causes abnormal dilatation of the heart. According to

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Mills, Liebigs Annalen 1863, Vol. 125, p. 71.

Kirchmann, Chemisches Zentralblatt 1876, p. 695.

Houdé, Journal de pharmacie et de chimie 1886, Vol. 13, p. 39.

Soldaini, Archiv der Pharmazie 1893, p. 321.

Kley, Chemisches Zentralblatt 1904, I, p. 123.

Willstaetter and Marx, Berichte der deutschen chemischen Gesellschaft Berlin 1904, II, p. 2351.

Laborde-Germain-Sée, Pharmazeutische Zentrallhalle 1886, p. 106. —

Archives de physiologie 1886. — Comptes rendus 1885, p. 1046.

— Gazette des hôpitaux 1885, p. 567.

Fick, Archiv für experimentelle Pathologie 1873, Vol. 1, p. 397.

Harnack-Meyer, *ibid.* 1880, Vol. 12, p. 392.

Dreser, *ibid.* 1888, Vol. 24, p. 234.

Meyer, *ibid.* 1893, Vol. 32, p. 106.

Cushny-Matthews, *ibid.* 1895, Vol. 35, p. 129.

Muto-Ishizaka, *ibid.* 1903, Vol. 50, p. 1.

Mitchell, Stenhouse, Philosophical Transactions 1861, II, p. 422.

Rymon, Thèse de Paris 1880.

Masius, Bulletin de l'Académie de médecine de Belgique 1887. —

Zentralblatt für die medizinischen Wissenschaften 1887, p. 978.

Langgaard, Therapeutische Monatshefte 1887, p. 229.

Kauenhowen, Dissertation Kiel 1892.

Thomas, Revue médicale de la Suisse romande 1899, p. 725.

Garand, Thèse de Paris 1886.

Griffé, Thèse de Nancy 1886.

Dontas, Archives internationales de physiologie 1905, p. 72.

Gluzinski, Przegląd lekarski 1887, No. 1.

Barton, Journal of the American Medical Association 1910, Vol. 55, p. 248.

Kobert, sparteine, like the digitalis products, belongs to the class of drugs which raise blood pressure and increase the rate of circulation. But whereas the digitalis products are placed by the author among those drugs which increase the tone of the heart and blood vessels, he places sparteine among the drugs which increase the heart's capacity for work. Sparteine deserves full consideration from a therapeutic standpoint, if only because it is relatively slightly toxic. It may be prescribed in those cases in which digitalis medication has to be suspended, in order to avoid cumulative action, provided there is no urgent danger and an immediate action is not required. The slight toxicity of the alkaloid is well shown by an experiment of Griffé's; he took 0.4 gramme (6 grains) of sparteine sulphate without evil consequences, apart from a sensation of dulness in the head.

Laborde and Germain-Sée found that the subcutaneous injection of sparteine increases the pulse rate and frequency of respiration, strengthens the cardiac action and rapidly restores the disturbed cardiac rhythm; this is said to be noticed particularly in severe atony of the myocardium with retardation of the cardiac contractions. According to the clinical tests of Gluzinski, sparteine acts very rapidly in badly compensated cardiac lesions, in which it has a good effect on the pulse and the subjective symptoms. He gave it internally in doses of 0.1 gramme ( $1\frac{1}{2}$  grains). In general, however, he only advises the use of sparteine in cases in which digitalis is contra-indicated, if the action of digitalis cannot be waited for and if insufficient cardiac activity has led to troublesome symptoms. Clarke came to the same conclusions as a result of his clinical investigations. Following the use of single internal doses of 0.01 to 0.015 gramme ( $\frac{1}{6}$ — $\frac{1}{4}$  grain) an action was observed after 30 to 40 minutes and lasted for 4 to 5 hours, after which period the dose had to be repeated. In his experience this could be easily carried out, because daily doses amounting to as much as 0.7 gramme (10 grains) occasioned no toxic symptoms. Clarke also confirmed the action of sparteine sulphate in increasing the rate of respiration.

According to Stössel, sparteine sulphate probably has the same action as digitalis qualitatively, but not quantitatively.

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Kobert, *Pharmakotherapie* 1908, p. 342.

Clarke, *American Journal of Medical Sciences* 1887, p. 363.

Stössel, *Zentralblatt für die gesamte Therapie* 1887, p. 163.

It has, however, no diuretic effect. This was also pointed out by Frömüller, who considered scoparin to be the component of broom having the diuretic action. This author, also, looks upon sparteine as a supplementary drug in cases in which digitalis is not well tolerated. Prior, on the other hand, recommends its use if digitalis fails, or if it be desirable to quickly regulate the cardiac action. For this purpose doses of 0.1 gramme ( $1\frac{1}{2}$  grains) should be used. Larger doses should be avoided, as they are liable to cause the return of irregularity of the cardiac rhythm, which had before been regulated.

The rapid action of sparteine, insisted upon by the observers mentioned above, was doubted by Kurloff and Lewaschew, for by measuring the blood pressure in patients and making sphygmographic records they were only able to perceive an action on the heart after 12 hours. Both authors, however, admit that the preparation has a beneficial effect on disturbances of compensation. Kurloff even states that he has observed\*) an increase in diuresis after the administration of sparteine, but with this Lewaschew does not agree. Lewaschew considers 0.1 to 0.3 gramme ( $1\frac{1}{2}$ —5 grains) of sparteine sulphate, given in 3 to 4 separate doses, to be the most reliable daily dose.

Thomas, in the course of his clinical studies, found that although the action of sparteine sulphate was similar to that of digitalis, it was slower and less intense. The drug is indicated in chronic myocarditis, asystole and subjective troubles, and also in cardiac debility and arrhythmia. Internally, as well as subcutaneously, it may be administered 3 times a day in doses of 0.05 gramme ( $\frac{3}{4}$  grain).

On account of the relatively slight toxicity of sparteine, it is scarcely possible to fix a maximum dose. In the literature 0.03 gramme ( $\frac{1}{2}$  grain) and 0.1 gramme ( $1\frac{1}{2}$  grains)

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Frömüller, *Memorabilien* 1878, p. 535.

Prior, *Berliner klinische Wochenschrift* 1887, p. 661.

Kurloff, *Archiv für klinische Medizin* 1889, Vol. 45, p. 57.

Lewaschew, *Zeitschrift für klinische Medizin* 1889, Vol. 16, p. 56.

\*) According to Rohde, increased diuresis is the rule after 3 to 4 doses of 0.01 gramme ( $\frac{1}{6}$  grain) a day. This treatment is also said to cause a decrease in albuminuria. (*Berliner klinische Wochenschrift* 1892, p. 815.)

Thomas, *Revue médicale de la Suisse romande* 1902, p. 197.

are given as the maximum single doses, 0.1 gramme ( $1\frac{1}{2}$  grains) and 0.5 gramme ( $7\frac{1}{2}$  grains) as the maximum daily dose.

Sparteine has been suggested for external use as an antipyretic by Geley and Guinard, and by Mollière and Vinay. According to these authors, the temperature can be considerably lowered in febrile diseases by painting with sparteine solution, in the same way as guaiacol is used; at the same time it has a beneficial effect on the skin eruptions in scarlet fever, small-pox, measles and erysipelas. In erysipelas, Mollière and Vinay state that they have obtained most brilliant results. In mild and medium cases the temperature was immediately reduced and the patients were cured within 2 to 3 days. In severe cases the temperature fell by  $1^{\circ}$  to  $1.5^{\circ}$  C. after painting with the preparation, the general condition was improved, the eruptions were limited and only in cases of leucocythæmia and cirrhosis did the disease run a severe course. The best time for applying the preparation by painting is when the temperature is not rising, e. g., in the evening. For this purpose a solution of 1 gramme (15 grains) of sparteine sulphate in 20 grammes ( $\frac{2}{3}$  oz) of water is used, which is only applied to healthy areas of the skin, which are then protected by a light bandage.

### Strophanthin.

The strophanthus plant is a member of the natural order Apocynaceæ, indigenous to tropical Africa, Madagascar and the Malay Archipelago, the botanical species of which has not yet been definitely determined. No less than 40 different species of strophanthus are known. According to Braun, 5 varieties have been found in German East Africa alone. A large amount of literature has been published relating to the derivation of strophanthus seeds, their action and use and the strophanthin prepared from them, which cannot be quoted here. Reference will therefore be made to the more important works and allusions in the literature, which are necessary for the consideration of this subject:

Gilg, E. Die Strophanthusfrage. Arbeiten aus dem pharmazeutischen Institut der Universität Berlin 1905, p. 60. — Über die pharmakognostisch wichtigsten Strophanthusarten. Der Tropenpflanzer 1902, p. 551.

Geley-Guinard, Semaine médicale 1894, p. 504.

Mollière-Vinay, Lyon médical 1896, No. 3 and 4.

- Meyer, Über Samen Strophanthi. Archiv der Pharmazie 1907, Vol. 245, p. 351.
- Hartwich, Realenzyklopaedie der gesamten Pharmazie 1908, Vol. XI, p. 633.
- Engler, Monographien afrikanischer Pflanzenfamilien, VII, Strophanthus. Compiled by E. Gilg, Leipzig 1903.
- Thoms, Die Strophanthusfrage vom chemischen Standpunkte. Arbeiten aus dem pharmazeutischen Institut der Universität Berlin 1905, p. 73.
- Husemann, Strophanthus. Pharmazeutische Zeitung 1887, No. 50 and 51.
- Fraser, Strophanthus. Transactions of the Royal Society of Edinburgh 1891, Vol. 35. — British Medical Journal 1887, p. 151 and 171.
- Pins, Wirkung der Strophanthussamen. Therapeutische Monatshefte 1887, p. 209 and 261.
- Langgaard, Wirkung der Strophanthussamen. Therapeutische Monatshefte 1887, p. 306.
- Drasche, Wirkung des Strophanthus. Zentralblatt für die gesamte Therapie 1887, p. 347.
- Hochhaus, Strophanthustinktur. Deutsche medizinische Wochenschrift 1887, p. 309.
- Denian, German and English publications on Strophanthus. — Bulletin général de thérapeutique 1887, p. 168, 220, 271.
- Holmes, Commercial Varieties of Strophanthus. Pharmaceutical Journal 1893, p. 868, 927, 1906, p. 312.
- Braun (Amani) Der Pflanze 1910, Vol. 6, p. 291. (Die Strophanthusarten von Deutsch Ost-Afrika.)

In recent years special attention has been paid in therapeutics to two kinds of strophanthus seeds, the Kombé seeds of Strophanthus Kombé Oliver, from which I isolate a morphous strophanthin. puriss., and the Gratus seeds of Strophanthus Gratus Wall and Hook, from which I prepare the crystalline Gratus-strophanthin. These two strophanthins are two totally different bodies and must therefore under no circumstances be substituted for one another in prescribing and dispensing. In order to avoid confusion it would be better if in place of the names used hitherto for these two strophanthins, the designations "Gratus-strophanthin" and "Kombé-strophanthin" were introduced.

With regard to the chemistry and physiology of the strophanthins, reference should be made to the following literature:

- Hardy-Gallois, Journal de pharmacie et de chimie 1877, I, p. 177.
- Arnaud, Comptes rendus (1888) Vol. 106, p. 1011 and Vol. 107, p. 179.

- Fraser, *Pharmaceutical Journal* Vol. 16, p. 109, Vol. 18, p. 6 and 69, Vol. 20, p. 328.  
Kohn-Kulisch, *Berichte der deutschen chemischen Gesellschaft* 1898, p. 514.  
Feist, *ibid.* 1898, p. 534, 1900, p. 2063 and 2091.  
Gottlieb-Magnus, *Archiv für experimentelle Pathologie* 1904, Vol. 51, p. 30.  
Fraenkel, *ibid.* 1904, Vol. 51, p. 84.  
Magnus-Sowtons, *ibid.* 1910, Vol. 63, p. 255.  
Kasztan, *ibid.* 1910, Vol. 63, p. 406.  
Loew-Zerner, *Wiener medizinische Wochenschrift* 1887, p. 1171.  
Paschkis-Zerner, *Wiener medizinisches Jahrbuch* 1887, p. 513.  
Popper, *Zentralblatt für Medizin* 1888, p. 418.  
Reusing, *Dissertation Würzburg* 1889.  
Werschinin, *Archiv für experimentelle Pathologie* 1909, Vol. 60, p. 328.  
Heffter, *Therapeutische Monatshefte* 1909, p. 45.  
Straub, *Therapeutische Monatshefte* 1910, No. 3.  
Fraser, *British Medical Journal* 1885, p. 904.

1. Kombé-Strophanthin = k-Strophanthin = Strophanthin. puriss. amorph.

The amorphous strophanthin, prepared from the seeds of *Strophanthus Kombé*, is a yellowish powder, soluble in water and alcohol.

The work of Th. R. Fraser on the pharmacological and therapeutic action of strophanthus and the strophanthins was instrumental in influencing the introduction of strophanthin into therapeutics. According to the minute investigations of this author, small doses of strophanthin especially prolong diastole, while large doses prolong systole\*). But strophanthin always brings about an increase in cardiac activity and retardation of the pulse. Its action on the heart is considerably stronger than that of the digitalin of commerce, but weaker with regard to the constriction of the blood vessels. This property of not causing narrowing of the lumen of the vessels, which is also confirmed in the communications of Popper, Langgaard, Paschkis and Zerner and others, was considered by Fraser to be an advantage of strophanthin medication in cardiac lesions over digitalin. But Kobert, Kakowski and Günther came

\*) Compare Gottlieb, *Therapeutische Monatshefte* 1911, p. 10.  
Popper-Langgaard-Zerner, *l. c.*

Kobert, *Lehrbuch der Intoxikationen* 1906, II, p. 1215.

Kakowski, *Archives internationales de pharmacodynamie* 1905, p. 43.

Günther, *Therapeutische Monatshefte* 1904, p. 285.

to the conclusion that strophanthin also caused constriction of the vessels. However this may be, Fraser's experiments on man, using the internal administration or the subcutaneous injection of 0.001 gramme ( $\frac{1}{64}$  grain) of strophanthin, certainly led to a considerable improvement in the circulation, increase in diuresis, and the disappearance of œdema, dyspnœa and palpitation, which proved the value of strophanthin.

Rothziegel found that a dose of only 0.0003 gramme ( $\frac{1}{200}$  grain) of strophanthin strengthened the pulse in about 5 to 10 minutes. Although the removal of arrhythmia and the increase in diuresis took effect somewhat later than when digitalis is used, the result lasted longer. As the author held the view that strophanthin possessed no cumulative action\*) whatever, he usually prescribed it in single doses of 0.0003 gramme ( $\frac{1}{200}$  grain) and in daily doses of 0.001 to 0.003 gramme ( $\frac{1}{64}$ — $\frac{1}{20}$  grain); subcutaneously, especially in cardiac debility, he used doses of 0.0005 gramme ( $\frac{1}{125}$  grain), by which means he effected a rapid strengthening of the heart. Schulz's discovery that the patient does not become habituated to strophanthin is also of importance, but the clinical appreciation of the glucoside was due to the communications of A. Fraenkel, which instigated a number of investigators to study strophanthin therapeutically.

Fraenkel prefers the intravenous application of strophanthin to other methods, as it possesses many advantages. The action is more rapid than that following its internal, subcutaneous or intramuscular exhibition, and the whole situation may be changed in a few minutes. In spite of smaller dosage, the results are certain, while no intestinal disturbances need be feared. Thus the physician, by the aid of intravenous strophanthin injection, is in quite a different position than was

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Rothziegel, Wiener klinische Wochenschrift 1890, p. 1787.

\*) Flesch does the same (Wiener klinische Wochenschrift 1908, No. 46).

Schulz, Vierteljahresschrift für gerichtliche Medizin 1891, Vol. 21, No. 2.

Fraenkel, Therapie der Gegenwart 1907, p. 56. — Archiv für experimentelle Pathologie 1907, Vol. 57, p. 79. — The author used for his experiments k-Strophanthin Boehringer.

formerly the case in the presence of even severe, acute compensatory disturbances, and with this agent he is generally in a position to appreciate the exact condition of the patient and to relieve his symptoms, which are often most distressing. Fraenkel's method is excellent in all cases of threatening cardiac debility, in which the sudden failure of the circulation does not depend on insufficiency of the kidneys and blood vessels, but is of cardiac origin. It is also indicated in all cases of acute and chronic cardiac insufficiency, in which speedy treatment is desirable, even though there be no immediate danger. A single injection often suffices in these cases to effect lasting compensation. Should this not occur, i. e., if the effect is only transitory, the internal administration of digitalis may be begun within the following 24 hours; by this means the digitalis action begins as the strophanthin action ceases, and thus the disadvantages of a latent period are circumvented. The intravenous injection is valuable, also, in cases exhibiting an idiosyncrasy to digitalis, or in which the internal administration of digitalis products is contra-indicated by the condition of the gastro-intestinal tract. Care is advisable if the patient is still under the influence of digitalis, for in spite of the assertions of several authors (compare above) it cannot be considered as proved that strophanthin has no cumulative action. Fraenkel suggests 0.001 gramme ( $\frac{1}{64}$  grain) as an effective single dose, which is dissolved in 1 c.c. (17 min.) of normal saline solution and injected intravenously. In severe cardiac debility, in the moribund, this amount should not be given in one dose, but in two injections in the course of an hour. The intravenous injections of strophanthin, if correct technique is employed and the solutions are properly sterilised, should practically never cause by-effects. But it should be noted in using strophanthin that injections should not be given too frequently or in too large doses in order to force an effect, especially not in unsuitable cases. The dose of 0.001 gramme ( $\frac{1}{64}$  grain), according to Fraenkel, should not be repeated within 24 hours.

Strophanthin is also very useful in congestive conditions, in which an injection of 0.001 gramme ( $\frac{1}{64}$  grain) causes considerable diuresis and alleviates the symptoms more rapidly and for just as long as does a course of digitalis treatment of several days.

In testing Fraenkel's method, very good results were obtained by R. von den Velden, H. Starck, L. Schönheim, A. Hasenfeld, M. Hedinger, Baccelli, Lust, Ch. Höpfner, O. Hornung, Flesch, Danielopolu, Crispoli and Pennesi.

According to Hasenfeld, strophanthin acts even in those cases in which other drugs have failed, but only provided the heart has still a certain amount of power, otherwise this drug also fails. In circulatory disturbances with high blood pressure, caution is, in his opinion, necessary. He considers it advisable in these cases to perform venesection before giving the strophanthin.

Hedinger points out that only the œdema due to cardiac insufficiency is improved by strophanthin, so that the result of injecting strophanthin into a dropsical patient may prove useful in diagnosing the etiology of the disease.

Baccelli, in treating the paroxysms of essential tachycardia, used a solution of 0.001 gramme ( $\frac{1}{64}$  grain) of strophanthin in 10 c.c. ( $\frac{1}{3}$  oz) of normal saline solution. Of this 5 c.c. (85 min.), injected intravenously in threatened stoppage of the heart, acted almost instantaneously.

Hornung is of the opinion that as much as 0.0015 gramme ( $\frac{1}{40}$  grain) of strophanthin may be injected in the course of a day, and that this amount may be prescribed without fear for a prolonged period, for in one of his cases he gave 0.0085 gramme ( $\frac{1}{8}$  grain) within a week.

Crispoli found that in severe disturbances of compensation strophanthin did not act when given internally, whereas intravenous injections acted at once. Intramuscular injections

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Velden, *Münchener medizinische Wochenschrift* 1906, p. 2137.

Starck, *Deutsche medizinische Wochenschrift* 1907, p. 451.

Schönheim, *Wiener medizinische Presse* 1907, No. 39.

Hasenfeld, *Budapesti Orvosi Ujsag* 1906, No. 51.

Hedinger, *Münchener medizinische Wochenschrift* 1907, p. 2020.

Baccelli, *Gazzetta degli ospedali e delle cliniche* 1907, No. 80.

Lust, *Deutsches Archiv für klinische Medizin* Vol. 92, No. 3 and 4.

Höpfner, *ibid.* No. 5 and 6.

Hornung, *Münchener medizinische Wochenschrift* 1908, p. 2044.

Flesch, *Wiener klinische Wochenschrift* 1908, p. 1590.

Danielopolu, *Revista scintelor medicale* 1910, February.

Crispoli, *Policlinico* 1909, No. 6.

Pennesi, *ibid.*

take effect somewhat less rapidly and surely, but they are useful in cases of medium severity. Only in nephritis and arterio-sclerosis does he consider that strophanthin should not be used. According to Pennesi, the injections are of special value in congestion of the lesser circulation, as for example in emphysema. But in these cases the action should at the latest become manifest after the second injection; if this is not the case, the continuation of this treatment is of no value.

In an interesting experimental work by Vagt on the action of intravenous injections of strophanthin in health and disease, it is stated that doses of 0.001 gramme ( $\frac{1}{64}$  grain), given to healthy individuals, have no effect on the peripheral vessels, although they always exercise a distinct but moderate action on the heart, and cause a transitory rise in the blood pressure. But in patients suffering from severe loss of compensation they act powerfully on the force of the beat, its regularity, equality and frequency; thus the diseased heart, in certain circumstances, is more susceptible to strophanthin than is the healthy organ.

While several of the authors mentioned above decline to use injections of strophanthin, not only on account of their slower action, but more especially on account of the pain they cause, Kontschalowski has come to the conclusion that solutions of strophanthin, given in therapeutic doses, do not cause more pain than does the injection of any other preparation, which is painless in itself. Its action on cardiac activity and diuresis, except in one case of paroxysmal tachycardia, could always be observed within a short time and lasted at least 3 hours, and sometimes as long as a week. The author recommends the injection of strophanthin whenever a rapid action is desired, as for example in acute asystole in uræmia and in infective diseases. A. K. Stone has also obtained very satisfactory results with intravenous injections of strophanthin in conditions of collapse occurring in the course of pneumonia. If in these cases digitalis has not previously been administered, the author considers that doses of 0.001 gramme ( $\frac{1}{64}$  grain) should be given, for in a case

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Vagt, Medizinische Klinik 1909, No. 49—51.

Kontschalowski, Medizinskoe Oboshrenie 1909, No. 6.

Stone, Boston Medical and Surgical Journal 1909, No. 8, (19th August).

which received half this amount only a transitory success was obtained.

Strophanthin is relatively seldom given internally, as it does not act with sufficient rapidity, and because it occasionally has an unpleasant, irritant effect on the gastro-intestinal tract. Renault, however, did not observe this action. In a case of cardiac debility he prescribed a solution of 0.0025 gramme ( $\frac{1}{25}$  grain) of strophanthin in 200 grammes ( $6\frac{2}{3}$  oz) of water, of which a tablespoonful was taken daily for a considerable time, without causing any undesirable by-effects. Pédebidon, Barié, Catillon, Hirtz and Schneider, who in contra-distinction to the authors named above consider that the intravenous injection of strophanthin is not free from danger and is only to be used in exceptional cases, are more in favour of the internal administration of the drug. By giving correspondingly large doses, they consider that as rapid a result can be obtained by this method. Vaquez doubts this and only considers the intravenous injection to be of real value. In his opinion the cases of death attributed to the intravenous method of administration are no reason for giving up such a useful form of treatment. Liebermeister attributes these accidents to the cumulative action of strophanthin, and they can therefore be avoided if sufficient attention be paid to this effect. In threatening cardiac insufficiency 0.7 to 1 milligramme ( $\frac{1}{90}$ — $\frac{1}{64}$  grain) is given at once, but not more than 1 milligramme ( $\frac{1}{64}$  grain) in 24 hours, and not more than 1.5 milligrammes ( $\frac{1}{40}$  grain) in 48 hours. In less threatening cases smaller doses are given at the beginning. If the patient has taken digitalis preparations before the commencement of the strophanthin medication, an interval of 4 days should be left between the last dose of digitalis and the first injection of strophanthin. It is of no use in obstinate cases to attempt to reduce the pulse rate by giving too frequent or too large doses.

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Renault, *Journal de médecine* 1907, No. 51.

Pédebidon, *Berliner klinische Wochenschrift* 1909, p. 1703.

Barié, Hirtz and Schneider, *Münchener medizinische Wochenschrift* 1909, p. 1766.

Catillon, *Münchener medizinische Wochenschrift* 1909, p. 739.

Vaquez, *Presse médicale* 1909, p. 228. — *Journal médical français* 1911, No. 3, p. 125.

Liebermeister, *Medizinische Klinik* 1908, Supplement No. 8, 1909, Supplement No. 12. — *Therapie der Gegenwart* 1908, No. 12.

The dose for injection is sufficiently clear from what has been said. As regards the internal dosage of strophanthin, probably on account of unnecessarily great caution, only small doses of 0.0001 to 0.0003 gramme ( $\frac{1}{640}$ — $\frac{1}{200}$  grain), and daily doses of 0.001 gramme ( $\frac{1}{64}$  grain) have found favour. These doses appear very small, when it is considered that the dose for injection is either larger or just as large, and that the preparation acts less powerfully when administered internally.

Like most bodies of the digitalin group, strophanthin has an anæsthetic action, which has, however, found but slight consideration in therapeutics. As far as I know, E. Steinach was the first to draw attention to this action, and Panas confirmed the fact that strophanthin, when applied to the conjunctiva of rabbits, produced anæsthesia in a short time, and which lasted for several hours. In man, however, its application causes inflammation of the conjunctiva, so that in the author's opinion there is little likelihood of its being used in ophthalmic practice.

In veterinary medicine strophanthin is used with success in cardiac debility and dropsical symptoms. As its internal administration has a less pronounced diuretic action than its subcutaneous or intravenous exhibition, the latter methods are usually preferred. Uebele advises the following dosage: For a horse, internally 0.05 to 0.15 gramme ( $\frac{3}{4}$ — $2\frac{1}{3}$  grains) (up to 0.00002 gramme [ $\frac{1}{3200}$  grain] for every kilogramme of body weight), subcutaneously 0.002 to 0.003 gramme ( $\frac{1}{32}$  to  $\frac{1}{20}$  grain), intravenously 0.0005 to 0.002 gramme ( $\frac{1}{125}$ — $\frac{1}{32}$  grain); for a sheep or a goat, subcutaneously 0.00002 gramme ( $\frac{1}{3200}$  grain) for every kilogramme of body weight; for a dog, internally 0.00017 to 0.0004 gramme ( $\frac{1}{400}$ — $\frac{1}{160}$  grain), subcutaneously 0.00025 to 0.001 gramme ( $\frac{1}{250}$ — $\frac{1}{64}$  grain), (up to 0.00004 gramme [ $\frac{1}{1600}$  grain] for every kilogramme) and intravenously 0.000002 gramme ( $\frac{1}{32000}$  grain) for every kilogramme of body weight. According to Regenbogen, non-toxic doses given to healthy domestic animals cause slowing of the pulse rate and tension of the arterial walls. If the treatment is continued for a short time the pulse

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Steinach, Wiener klinische Wochenschrift 1888, No. 21 and 22.

Panas, Bulletin de l'académie de médecine 1890, p. 261.

Uebele, Handlexikon der tierärztlichen Praxis 1910, p. 452.

Regenbogen, Monatshefte für prakt. Tierheilkunde 1904, No. 10.

becomes fuller and stronger and after some days the amount of urine excreted is considerably increased. Occasionally also drowsiness, languidness and insensibility make their appearance. After the administration of strophanthin to animals affected with various cardiac lesions, the author observed a good effect on the pulse and respiration, which was accompanied by an improvement in the general condition and by increased appetite. A case of acute pneumonia with great cardiac debility was cured by the use of strophanthin alone. In nephritis the regular administration of the drug caused a decrease in the albuminuria. In cardiac lesions and their consequences, the author recommends the subcutaneous injection of aqueous solutions. As a dose for a horse he suggests 0.002–0.003 gramme ( $\frac{1}{32}$ – $\frac{1}{20}$  grain), and for dogs 0.00025 to 0.001 gramme ( $\frac{1}{250}$ – $\frac{1}{64}$  grain).

2. *Gratus-Strophanthin* = *g-Strophanthin* =  
*Strophanthin. crystallisatum* = *Ouabaïn.*  
*crystallisatum*.

G-strophanthin is a glucoside having the chemical formula  $C_{30}H_{46}O_{12} + 9H_2O$ , and is obtained from the seeds of *Strophanthus Gratus* Franch., a member of the Apocynaceæ indigenous to tropical Africa. It forms white crystals, soluble in water and alcohol\*), and without a definite melting point. The preparation dried at 100° C. sinters at about 185°, softens at about 200° C. and decomposes at about 215° C. with the formation of bubbles.

The preparation and properties of g-strophanthin were first described in detail by H. Thoms, for which reason I also place this preparation on the market under the designation “strophanthin. crystallisatum acc. to Thoms”. With regard to the description of this preparation, I must refer those interested to the original paper by Thoms. But it may be noted that the author’s investigation has proved the chemical identity of g-strophanthin (Thoms) with ouabaïn (crystallisatum), already isolated by Arnaud from the wood of ouabaio\*\*).

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\*) At 15° C. it dissolves in about 100 parts of water and in about 30 parts of absolute alcohol or amyl alcohol. It dissolves with difficulty in ether and chloroform.

Thoms, *Berichte der deutschen pharmazeutischen Gesellschaft* 1904, p. 104.

\*\*) Compare the article “Ouabaïn” p. 101.

Werschinin, who tested g-strophanthin pharmacologically, came to the conclusion that when applied dissolved in Ringer's solution, in the same concentration, it had a similar action whether administered endocardially or exocardially. The weaker concentrations cause stoppage of the heart in diastole, medium concentrations lead to stoppage in systole, while strong concentrations again cause stoppage in diastole, to which paralysis of the heart is presently associated. The concentration of strophanthin causing stoppage in systole varies from 1:1000 to 1:50,000, provided the poison be given dissolved in Ringer's solution. In addition, the action is accelerated by blood serum, this depends on lipoid-like substances contained in the blood serum. The occurrence of stoppage in systole is also hastened by the presence of calcium salts in the blood serum. Even in a dilution of 1:2,500 calcium chloride hastens stoppage in systole, so that doses of strophanthin usually having a diastolic action cause stoppage in systole. The last-named action, however, can only be observed when it is employed endocardially. A communication of Krailsheimer, according to which g-strophanthin has the same pharmacological action as digitoxin, is of special interest with regard to the action of strophanthin.

According to H. Schedel, g-strophanthin is of considerable therapeutic value in all debilitated conditions of the heart, such as occur in convalescence from disease, or in consequence of valvular disease and atrophy of the muscle. It accelerates the cardiac activity, has a beneficial influence on dyspnoea, raises the blood pressure and increases diuresis, and assists in the elimination of oedema. Even though it cannot be used to replace digitalin in severe cases, it has the following advantages over the latter: 1. It acts more rapidly, its action generally being apparent in a few hours. 2. It can, if necessary, be given subcutaneously. 3. Even when it has been employed for weeks it shows fewer unpleasant by-effects than digitalin and its cumulative properties become evident at a later period; but on account of its rapid ab-

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Werschinin, Archiv für experimentelle Pathologie 1910, Vol. 63, p. 386.

Krailsheimer, Archiv für experimentelle Pathologie 1910, Vol. 62, p. 304.

Schedel, Berichte der deutschen pharmazeutischen Gesellschaft 1904, p. 120. — Zeitschrift für Krankenpflege 1905, No. 7.

sorption and the earlier appearance of slowing of the pulse the cumulative action can be earlier recognised and the administration of the drug discontinued in good time.

K. Hochheim reported upon the clinical tests for g-strophanthin, which were carried out at the Magdeburg-Sudenburg Hospital in the course of 12 to 15 months, and which permit a fairly reliable appreciation of the value of this medicament. It was prescribed as follows:

Rp. g-Strophanthin Thoms      0.03—0.06 gramme ( $\frac{1}{2}$ —1 grain)  
Syrup. aurant.                      20.0 grammes ( $\frac{2}{3}$  oz)  
Aq. destill.                      ad 200.0 grammes ( $6\frac{2}{3}$  oz)

Sig. One tablespoonful to be taken 3 to 6 times a day.

Hochheim obtained a very satisfactory result by the use of this medication in a case of aortic insufficiency, in which digalen and digitoxin had been tried without much benefit. By taking daily doses of 0.0125 to 0.025 gramme ( $\frac{1}{5}$ — $\frac{2}{5}$  grain) the patient's subjective symptoms were markedly improved within the first few days of the treatment. The sensation of fear and the palpitation disappeared and the appetite returned. The pulse, which had previously been continuously irregular, became regular within the first few days, and diuresis became normal. After the second day of treatment the urine was free from albumin. On the return of mild symptoms of congestion the use of suppositories containing 0.003 gramme ( $\frac{1}{20}$  grain) of g-strophanthin proved satisfactory. In severe disturbances of compensation, also, g-strophanthin rendered good service.

For cardiac debility in the course of infective diseases, Hochheim found that g-strophanthin was more efficacious in children than in adults. Children of 2 to 3 years of age were given daily doses of 0.002 gramme ( $\frac{1}{32}$  grain), and those of 10 years daily doses of 0.01 gramme ( $\frac{1}{6}$  grain). It was not only well borne, but proved a very useful drug in the treatment of cardiac debility in scarlet fever, diphtheria, and pneumonia.

The author places the maximum single dose for adults at 0.005 gramme ( $\frac{1}{12}$  grain), and the maximum daily dose at 0.03 gramme ( $\frac{1}{2}$  grain). It is, however, better to begin with smaller doses. Larger doses may cause diarrhoea with

bloody stools, vomiting, a feeling of oppression, headache and drawing pains in the region of the neck.

Whereas Hochheim prefers the internal administration of g-strophanthin to its intravenous injection and also considers that the former yields better results, G. Linzenmeier came to the conclusion that the internal administration of strophanthin is ineffective in severe disturbances of compensation, unless daily doses of 0.03 to 0.04 gramme ( $\frac{1}{2}$ — $\frac{2}{3}$  grain) are given for a prolonged period. The use of these doses, however, would entail the risk of cumulative action. Linzenmeier considers that the only advantage offered by the internal administration of g-strophanthin over that of digitalis preparations is that it alleviates the most distressing symptom, the dyspnoea, within a few hours, whereas the digitalis preparations effect this much more slowly, in the course of 1 to 2 days. Therefore, in the author's opinion, g-strophanthin should only be given internally when dyspnoea is the most prominent symptom, and then only as an introduction to a course of digitalis. It is, however, useful in less severe cases of cardiac insufficiency, in which a single daily dose of 0.03 to 0.04 gramme ( $\frac{1}{2}$ — $\frac{2}{3}$  grain) may be given. Here a beneficial effect may be produced in a few hours, especially on the dyspnoea, and, in certain circumstances, a single dose suffices to restore compensation. In these cases the action of g-strophanthin sets in earlier than that of the digitalis substances, but, according to Linzenmeier, it is not so prompt, so powerful or so lasting as the intravenous injection of g-strophanthin. The intravenous injections cannot be replaced by the internal exhibition in acute and threatening cardiac debility. The results of the investigations of Fleischmann and Wjasmensky are in agreement with this statement. In the experience of these authors, immediate and life-saving results may be achieved by the intravenous injection of 0.0005 gramme ( $\frac{1}{125}$  grain) of g-strophanthin in certain cases of chronic and acute circulatory disturbances, such as are not obtained with any other drug or by any other method. But if digitalis medication has already been adopted, care is necessary. In the case of moribund patients it should not be prescribed.

Linzenmeier, Dissertation Heidelberg 1909.

Fleischmann - Wjasmensky, Deutsche medizinische Wochenschrift 1909, No. 21.

Vaquez and Leconte have obtained good results, especially in pure myocarditis, by the use of g-strophanthin (given intravenously in doses of 0.0005 to 0.001 gramme ( $\frac{1}{125}$  to  $\frac{1}{64}$  grain) at intervals of 2 days), while its action in valvular lesions, particularly in aortic lesions, is apparently less pronounced. Vaquez expresses the same good opinion with regard to g-strophanthin as does Fleischmann.

#### Maximum Doses of the Strophanthins.

As the intensity of action of the strophanthins is much greater when injected into the circulation than when given by mouth, internal and intravenous (or subcutaneous) maximum doses should be strictly distinguished. According to the reports which have appeared with regard to the use of the strophanthins, the following may be taken as maximum internal doses:

for k-strophanthin as a single dose 0.0005 gramme ( $\frac{1}{125}$  grain) and 0.003 gramme ( $\frac{1}{20}$  grain) as a daily dose.

for g-strophanthin as a single dose 0.005 gramme ( $\frac{1}{12}$  grain) and 0.03 gramme ( $\frac{1}{2}$  grain) as a daily dose.

But these maximum doses really require revision, as it may be assumed that the maximum dose of k-strophanthin is too small\*) and that of g-strophanthin perhaps rather too large\*\*). In using the large doses it should always be borne in mind that for the sake of safety they should not be repeated on several consecutive days.

For intravenous, subcutaneous and intramuscular use, the maximum doses may provisionally be fixed as follows:

for k-strophanthin as a single dose 0.001 gramme ( $\frac{1}{64}$  grain) and 0.001 to 0.0015 gramme ( $\frac{1}{64}$ — $\frac{1}{40}$  grain) as a daily dose.

for g-strophanthin as a single dose 0.0005 gramme ( $\frac{1}{125}$  grain) and 0.001 gramme ( $\frac{1}{64}$  grain) as a daily dose.

Vaquez - Leconte, Bulletins et mémoires de la société médicale des hôpitaux de Paris 1909, No. 12. — Wiener klinische Wochenschrift 1909, No. 22. — Journal médical français 1911, No. 3, p. 125.

\*) Hatcher and Baily think it probable that the maximum dose of k-strophanthin, given internally, is approximately 0.01 gramme ( $\frac{1}{6}$  grain) and pro die 0.06 gramme (1 grain). They consider it better for the present, however, not to make use of the latter dose. Journal of the American Medical Association 1909, Vol. 52, p. 5.

\*\*) Compare Kobert, Intoxikationen 1906, II, p. 1215.

It may be noted, however, that the observation reported by Liebermeister is of importance with regard to the dosage of the strophanthins, namely that in febrile infective diseases larger doses of strophanthin are better borne than in afebrile diseases.

### Thevetin and Thevetosin.

Blas and de Vrij have isolated a glucoside, having the formula  $C_{54}H_{84}O_{24}$ \*), from the seeds of *Thevetia neriifolia*, of the natural order Apocynaceæ, indigenous to the West Indies; they named it "thevetin"\*\*\*). It forms colourless crystalline scales, with a bitter taste; melting point  $170^{\circ}C.$ , soluble in alcohol and hot water. On hydrolysis it is decomposed into sugar and theveresin.

Thevetosin was prepared by Herrera from the seeds of *Thevetia Yccotli*. It is a crystalline glucoside, soluble in alcohol, and which, like thevetin, may be regarded as a cardiac poison. Neither substance has attained therapeutic significance. (Compare article on the glucoside "Cerberid", page 87.)

### Urechites Suberecta.

The leaves of *Urechites suberecta* Jacq., a plant belonging to the natural order Apocynaceæ, were formerly used in the treatment of dropsy in the West Indies, where the plant is indigenous. The natives are also said to have prepared an arrow poison from the milk-juice of the plant. In his examination of the leaves of urechites, Bowrey found two crystalline bodies, urechitin and urechitoxin, and an amorphous substance, the so-called amorphous urechitoxin. None of these bodies has found favour in therapeutics. They cannot be obtained in the market.

Liebermeister, Medizinische Klinik 1909, Supplement No. 12, p. 265.

Blas, Bulletin de l'Académie royale de médecine de Belgique 1868, II, p. 745. — Neues Jahrbuch für Pharmazie 1869, p. 1 and 65.

de Vrij, Nederlandsch Tijdschrift voor Pharmacie 1884, p. 138.

\*) Compare Husemann, Archiv der Pharmazie 1876, I, p. 389.

\*\*) Thevetin and Thevetosin cannot be obtained in the market.

Herrera, Pharmaceutical Journal 1877, p. 854.

Bowrey, Chemical News 1878, Vol. 37, p. 166. — Journal of the Chemical Society 1878, Vol. 33, p. 252.

In order to decide the therapeutic value of the leaves of urechitis, Vowinckel and Langgaard experimented with a tincture prepared from them. According to these authors, urechitis exhibits the same cardiac action as digitalis, and in addition, especially in warm-blooded animals, an action on the peripheral nerves, which is apparent by convulsive symptoms. The authors also found it to possess an action antagonistic to curare. But this discovery is of no practical use, because the dose of urechitis necessary to counteract fatal poisoning by curare is in itself dangerous to life. Minkiewicz, in his pharmacological investigations, arrived at similar results.

I shall return to the consideration of the biological tests for digitalis and the bodies belonging to the digitalin group as soon as methods of testing are available which are generally accepted and free from objection, and the question of the physiological uniformity of the tests has been solved. Meanwhile I would refer those who are interested to the following passages in the literature:

Schmiedeberg, Archiv für experimentelle Pathologie 1910, Vol. 62, p. 303.

Gottlieb, Verhandlungen des 19. Kongresses für innere Medizin 1901, p. 21.

Focke, Therapie der Gegenwart 1904, p. 250. — Archiv für Pharmazie 1903, p. 128 and 687; 1907, p. 646; 1909, p. 545; 1910, p. 345 and 375. — Zeitschrift für experimentelle Pathologie und Therapie 1910, Vol. 7, p. 1; 1911, Vol. 9, p. 97. — Pharmazeutische Zeitung 1911, p. 358. — Berliner klinische Wochenschrift 1906, p. 642. — Vierteljahresschrift für gerichtliche Medizin und öffentliches Sanitätswesen 1906, Vol. 32, p. 130. — Therapeutische Monatshefte 1911, p. 533.

Lutzkaja, Archives internationales de pharmacodynamie et de thérapie 1908, p. 77.

Hale, American Journal of Pharmacy 1911, Vol. 83, p. 97.

Bickel, Medizinische Klinik 1911, p. 333.

Githens, Journal of the American Medical Association 1911, p. 606.

Freund, Medizinische Klinik 1909, No. 16.

Burmann, Wochenschrift für Chemie und Pharmazie 1910, p. 410.

Ziegenbein, Archiv der Pharmazie 1902, p. 454.

Straub, Zeitschrift für experimentelle Pathologie und Therapie 1905, Vol. 1, p. 489.

Vowinckel, Dissertation Berlin 1885.

Minkiewicz, Dissertation Dorpat 1889.

## Preparations and Drugs.

### Acetone.

The value of acetone in inoperable carcinoma of the uterus has been repeatedly emphasised by G. Gellhorn, who has had more than four years' experience of this drug\*). His original technique has been but little altered. After scraping the carcinoma with a sharp spoon, under an anæsthetic, the patient's pelvis is raised, the narcosis is discontinued and by means of a speculum 2 to 3 tablespoonfuls of pure acetone are poured into the cavity. The hæmorrhage ceases immediately, unless a large vessel has been opened, in which case a firm tampon should be applied. The blood-clot produced by the acetone is removed after 10 minutes, and the vulva is irrigated with water or corrosive sublimate solution; more acetone is poured in and after 20 minutes it is allowed to drain away, when irrigation with water or corrosive sublimate solution is repeated. Acetone is also used in the after-treatment. According to Gellhorn, the treatment is absolutely painless as long as the acetone does not come in contact with the vulva. To avoid this, the exterior of the speculum should be thickly coated with vaseline and after the acetone has drained away, plugs of cotton wool soaked in water should be repeatedly introduced into the cavity while the speculum is removed. The after-treatment is continued every 2 to 3 days for several weeks. In most cases the cavity diminishes in size so rapidly that smaller and smaller specula are necessary. After 6 to 8 weeks' treatment with acetone the author has frequently been unable to introduce anything larger than a catheter. In cases which run a favourable course one application of acetone weekly will suffice, but if the treatment is unsuccessful, or if the carcinoma shows a tendency to break down, curettage should be repeated after 4 to 6 weeks. The author was unable to observe better results by combining the acetone treatment with fulguration.

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Gellhorn, Zentralblatt für Gynäkologie 1911, p. 1240.

\*) Journal of the American Medical Association 1907, No. 17, 27th April. — Münchener medizinische Wochenschrift 1907, p. 2528. — Merck's Report 1907, p. 1 and 1910 p. 64.

As it is possible that by this treatment acetone might be absorbed, Gellhorn always examined the urine for acetone, but only found it present in very few cases. After a short interval in the treatment the acetone disappears from the urine, but even should it return, it has apparently no deleterious effect on the organism as a whole, for the general state of health, the appetite and the body weight always improve during treatment with acetone. The chief value of this treatment is not only that by its use the patient's life can be prolonged, but it also consists in the fact that the patients usually feel well.

Failures in this method of treatment may be due to the position of the carcinoma, the age and nationality of the patient, and to other factors at present unknown. Extensive recurrences, which are merely separated by a thin layer of tissue from the bladder and rectum, and carcinomata which have developed along the anterior partition as far as the vulva, are not particularly adapted for this mode of treatment, as there is difficulty in applying the acetone in such cases. In this case the solid acetone-sodium-bisulphite in powder may be used in place of liquid acetone; a thick layer should be applied with a suitable insufflator. Under the action of the secretions this salt is split up into its components and the acetone is enabled to act on the cancerous growth in a nascent state. According to Gellhorn, it is entirely non-irritant and can at least have a retarding influence on the carcinomatous growth.

### Acetone-Alcohol.

Mixtures of acetone and alcohol were used with very satisfactory results by Oeri and von Herff in their surgical practice as disinfecting agents for the hands of the operator, and for disinfecting the skin of the patient. Häberle's more recent experiments with a mixture of 30 parts of acetone and 70 parts of alcohol (95 p.c.) have confirmed the value of this mixture as a disinfectant. The author used for his experiments either very dirty hands or hands which had been directly infected by cultures of staphylococcus; he first cleansed the hands with soap and a nail brush for about 3 minutes and then wiped them with a piece of

Oeri—von Herff, Merck's Reports 1909, p. 85.

Häberle, Münchener medizinische Wochenschrift 1911, p. 1751.

flannel soaked in acetone-alcohol for 3 to 6 minutes. His results are reported to have been excellent. This procedure is said to sterilise the surgeon's hands for the time necessary to complete an operation.

Labhardt obtained very satisfactory results in midwifery practice when using acetone-alcohol as a disinfectant, and among his cases the number requiring operative measures was large, and the external conditions were frequently bad. According to his experience, this method yields at least as good results as the methods usually employed, and has the advantage of being very simple to carry out. Therefore the acetone-alcohol mixture may be recommended for use by midwives.

### Acetonitrile.

Acetonitrile (methyl cyanide,  $\text{CH}_3\text{CN}$ ) is a colourless, clear liquid with a characteristic odour; it is miscible with water and alcohol. The preparation has a specific gravity of 0.789 and boils at  $81^\circ$  to  $83^\circ\text{C}$ . No reliable data are to hand concerning the poisonous properties of the preparation. For example, whereas Maximowitsch considers methyl cyanide to be poisonous, as he was able to demonstrate that dogs succumbed after internal doses of 1.5 to 3 grammes, Lang considers it to be only slightly toxic, as rabbits bore doses of 1 gramme subcutaneously without harm. It is not yet certain that it is decomposed in the body, forming potassium cyanide, but it has been shown that about a fifth part of the methyl cyanide introduced into the body is excreted in the urine as an alkaline sulphocyanide. Therefore one part of the cyanogen residue is rendered innocuous by its combination with sulphur, but nothing is known of the fate of the other part, or of its physiological action. At any rate a cyanogen action has not yet been demonstrated with certainty. Reid Hunt and Trendelenburg, however, as-

Labhardt, Schweizer Rundschau für Medizin 1911, No. 25.

Maximowitsch, Petersburger medizinische Wochenschrift 1877, p. 325.

Lang, Archiv für experimentelle Pathologie 1894, Vol. 34, p. 247.

Reid, Hunt, Archives internationales de pharmacodynamie et de thérapie 1904, Vol. 12, p. 447. — Journal of Biological Chemistry 1905, I, p. 1. — Journal of the American Medical Association 1907, Vol. 49, p. 240.

Trendelenburg, Biologische Zeitschrift 1910, Vol. 29, p. 396.

sume that such action takes place, for in their experiments on animals they discovered interesting relations between methyl cyanide and certain glandular secretions. Their researches showed that animals which had been fed on thyroid gland could tolerate more acetonitrile than others, so that it seems permissible to assume that thyroid gland substance neutralises the toxic action of acetonitrile. G. Ghedini has shown that the resistance of white mice to the action of subcutaneous injections of acetonitrile is increased when its toxic action is neutralised in this way. Ghedini found that 5 milligrammes of acetonitrile were fatal to a white mouse. But if the mice were fed for 9 days with the blood of patients suffering from Graves' disease, they remained alive when given the quantity of acetonitrile mentioned above. This experiment was also successful when the mice were fed with blood from patients who were suffering not from Graves' disease, but from other diseases, e.g., from several uræmic patients, two patients with enlarged thyroids, which were no doubt associated with hypersecretion, and one patient with *adipositas dolorosa*; in all these cases a connection of the disease with the thyroid gland may be assumed. It is uncertain to what this increased power of resistance or "Ghedini's reaction" is due. Possibly the decomposition of the methyl cyanide is retarded or the prussic acid which has been split off is altered by oxidation into less poisonous substances. In any case it is impossible to deny that the reaction has a certain diagnostic value, for Ghedini obtained an absolutely negative acetonitrile reaction in two patients who showed no definite symptoms of Graves' disease, and which had been tentatively diagnosed by the clinician as pseudo-Graves'; whereas other patients with typical symptoms of Graves' disease gave an absolutely positive result. It may therefore be assumed that Ghedini's reaction, when it has been further worked out and investigated, will prove of importance in the diagnosis of Graves' disease.

### Actinium.

The success of radium in therapeutics gave an impetus to the search for substitutes, especially as the supply of radium salts is attended by ever increasing difficulties. Therefore

latterly, besides using thorium, trials have been made with actinium and mesothorium\*).

Actinium, which was discovered in 1899 by A. Debierne in uranium pitchblende residues and is identical with the emanium described by F. Giesel, is similar to thorium in its radio-active properties, but surpasses it considerably in activity. In its commercial form it is a brownish-red, granular powder, soluble in hydrochloric acid and in nitric acid, insoluble in water.

The first clinical tests with actinium were carried out by V. Czerny and A. Caan, who investigated its use in the treatment of malignant growths. For this purpose the authors injected an emulsion of actinium in normal saline solution (for instance 0.5 of actinium to 10 of solution), whereby the actinium remained as a radio-active deposit at the place of injection. They commenced with intramuscular injections of 0.01 gramme ( $\frac{1}{6}$  grain) and gradually increased the dose to 0.1 to 0.2 gramme ( $1\frac{1}{2}$ —3 grains) of actinium. The injection was made every second day, usually in the early morning, as occasionally a strong reaction (swelling, redness, rise of temperature) was observed to occur about 8 to 10 hours later. No other unpleasant by-effects were observed, except in one case, in which there was a transitory rigor.

The cases treated by actinium included recurrent carcinoma of the breast, carcinoma of the rectum, lymphosarcoma, a branchiogenous carcinoma, a sarcoma of the orbit, and a myxosarcoma of the pelvis. Subjective and objective improvement followed in isolated cases, so that, in the authors' opinion, further trials with actinium are justified. Even if the results obtained by this drug are no better than those following the

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\*) Compare article on "Mesothorium" in this Report.

Debierne, *Comptes rendus de l'académie des sciences* 1899, Vol. 129, p. 593; 1900, Vol. 130, p. 906; 1904, Vol. 139, p. 538.

— *Physikalische Zeitschrift* 1905, Vol. 7, p. 14.

Giesel, *Berichte der deutschen chemischen Gesellschaft*, Berlin 1904, Vol. 37, p. 1696 and 3963. *Physikalische Zeitschrift* 1904, Vol. 5, p. 822. — Compare also: Brooks-Rutherford, *Physiological Magazine* 1904, Vol. 8, p. 373; Hartmann, *Physikalische Zeitschrift* 1904, Vol. 5, p. 570, 1905, Vol. 6, p. 401; Marckwald, *Berichte der deutschen chemischen Gesellschaft* Berlin 1905, Vol. 38, p. 2264; Hahn und Sackur, *ibid.* 1905, Vol. 38, p. 1943.

Czerny-Caan, *Münchener medizinische Wochenschrift* 1911, No. 34, p. 1801.

use of the radium preparations hitherto employed for the same purposes, they are certainly not inferior.

### Adalin.

Communications on the hypnotic action of this drug\*) were published in the past year by P. Schaefer, Flatau, S. Kalischer, E. Froelich, v. Boltensstern, R. Traugott, E. Scheidemantel, H. Hirschfeld, A. Eulenburg, G. Beyerhaus, Rehm, K. Singer, A. Kempner, Jung, Pelz, H. Hennes, Memelsdorf, E. Jennicke, M. Salomonski, O. Weiss, Lowinski, Claus, A. Fuchs, P. Reiss, H. Raschkow, A. Kaiser, M. Schultze, J. Hoppe and K. Seegers, E. Kobrak, O. Juliusberg, Raschkow and Fromm. According to

\*) Compare Merck's Report 1910.

Schaefer, Münchener medizinische Wochenschrift 1910, p. 2695.

Flatau, Deutsche medizinische Wochenschrift 1910, p. 2425.

Kalischer, Neurologisches Zentralblatt 1911, No. 1.

Froelich, Berliner klinische Wochenschrift 1911, p. 18.

Boltensstern, Deutsche Ärztezeitung 1911, p. 33.

Traugott, Berliner klinische Wochenschrift 1911, p. 300.

Scheidemantel, Münchener medizinische Wochenschrift 1911, p. 407.

Hirschfeld, Berliner klinische Wochenschrift 1911, p. 341.

Eulenburg, Medizinische Klinik 1911, p. 387.

Beyerhaus, Deutsche medizinische Wochenschrift 1911, p. 589.

Rehm, Therapie der Gegenwart 1911, p. 164.

Singer, Therapie der Gegenwart 1911, p. 190.

Kempner, Neurologisches Zentralblatt 1911, No. 6.

Jung, Deutsche zahnärztliche Zeitung 1911, No. 8.

Pelz, Zeitschrift für Neurologie 1911, No. 4.

Hennes, Zeitschrift für Neurologie und Psychiatrie 1911, No. 4.

Memelsdorf, Deutsche zahnärztliche Wochenschrift 1911, No. 6.

Jennicke, Psychiatrisch-neurologische Wochenschrift 1911, p. 466.

Salomonski, Deutsche medizinische Wochenschrift 1911, p. 637.

Weiss, Münchener medizinische Wochenschrift 1911, p. 1399.

Lowinsky, Therapie der Gegenwart 1911, p. 240.

Claus, Geneeskundig Tijdschrift 1911, No. 6.

Fuchs, Odontologische Nachrichten 1911.

Reiss, Psychiatrisch-neurologische Wochenschrift 1911, No. 18.

Raschkow, Medizinische Reform, 1911, Vol. 19.

Kaiser, Zahnärztliche Rundschau 1911, No. 26.

Schultze, Zahntechnische Rundschau 1911, No. 29.

Hoppe-Seegers, Therapie der Gegenwart 1911, No. 10.

Kobrak, Medizinische Klinik 1911, No. 43.

Juliusberg, Deutsche medizinische Wochenschrift 1911, No. 43.

Fromm, Deutsche medizinische Wochenschrift 1911, No. 45.

Raschkow, Deutsche medizinische Wochenschrift 1911, No. 49.

these authors, if not administered in too small quantities, it has a lasting action in the insomnia which occurs as a chief or partial manifestation of chronic neuroses, psycho-neuroses, in the course of neurasthenia, nervous conditions of depression and exhaustion, phobias, hysteria, melancholia during involution and commencing arterio-sclerotic dementia; and also in the insomnia associated with diseased conditions of the circulatory system, with Graves' disease, cardiac insufficiency, arterio-sclerosis, deprivation from morphine, and alcoholism. As a rule 0.75—1 gramme (12—15 grains) are said to produce the desired effect, but should the patient wake after having slept for several hours, another dose of 0.5 gramme ( $7\frac{1}{2}$  grains) may be given. By-effects have not as yet been observed; only when very large doses were given drowsiness was occasionally present on the following day. The sedative action of adalin was also tested by most of the above named authors. With few exceptions it displays a good effect in motor disturbances, paranoic conditions of excitement, phobias, psychic depression, irritative cardiac neuroses, sexual neurasthenia (erotic ideas, erections, masturbation), traumatic neuroses, neuroses consequent upon climacteric complaints, etc.

A special advantage of this drug lies in its prompt action and in the absence of cumulative properties. If rapid action is required, it is best given dissolved in warm fluids. But if a sedative action is principally desired adalin should be administered dissolved in cold water, in doses of 0.3—0.5 gramme ( $5\text{--}7\frac{1}{2}$  grains) several times a day; thus its sedative action then lasts longer.

Adalin has also been tried in epilepsy, but whether it is of more use in this affection than other preparations of bromine remains to be proved. On the other hand, in pertussis its usefulness has been demonstrated, at least in mild cases as a sedative for the nervous symptoms of whooping-cough. As a hypnotic the dose for babies under one year is 0.2 gramme (3 grains) of adalin given every other evening, for children of 1 to 12 years, 0.2—0.6 gramme (3 to 9 grains). For babies of 3 months 0.15 gramme ( $2\frac{1}{2}$  grains) on an average may be given. On account of its harmlessness adalin may safely be used as a sedative and hypnotic for children, and more especially for nervous, restless children, for those suffering from insomnia on account

of infective diseases or of dyspeptic symptoms, and for mild convulsions due to various causes.

Adalin is ineffective in severe pain, but may be used with advantage to calm the patient before operations, especially in extraction of teeth. But it must be given at a suitable time, in order that the patient may be under the influence of the drug during the operative procedure. According to Memelsdorf, 20 to 30 minutes should be allowed for the action to take place. Adalin has likewise been found useful, in doses of 0.5 to 1 gramme ( $7\frac{1}{2}$ —15 grains), for the after-treatment of sensitive patients.

### Adrenalin.

In severe conditions of collapse, the fall in blood pressure has been successfully controlled on various occasions recently by injections of adrenalin. At first the drug was administered intravenously, but of late the subcutaneous method has been more largely employed. Kirchheim found in his experiments that adrenalin, when injected subcutaneously, is perfectly harmless, and may be given in comparatively large doses. He prescribed it in ordinary cases in doses of 0.0005—0.001 gramme ( $\frac{1}{125}$ — $\frac{1}{64}$  grain) at intervals of 1 to 2 hours; in very severe cases of collapse even in doses of 0.002—0.003 gramme ( $\frac{1}{32}$ — $\frac{1}{20}$  grain). He fixed 0.004—0.006 gramme ( $\frac{1}{16}$  to  $\frac{1}{10}$  grain) as the daily dose for adults and children. The author, however, reports cases in which he gave daily doses of 0.012—0.032 gramme ( $\frac{1}{5}$ — $\frac{3}{5}$  grain). The total amount of adrenalin used during a cure was 0.08—0.4 gramme, ( $\frac{1}{3}$  to 6 grains), and in no case did he observe any bad effects. The treatment with adrenalin is especially indicated in infective diseases such as scarlet fever, diphtheria, and pneumonia, in which Kirchheim has been able to save life in cases which were apparently moribund.

Von den Velden also is in favour of the subcutaneous employment of adrenalin in circulatory disturbances. He even regards the intravenous injection of the drug as dangerous, and only justifiable if the necessity arises to stimulate the circulation even at the risk of a fatal issue, as for example in the collapse of anæsthesia.

Kirchheim, Münchener medizinische Wochenschrift 1910, p. 2694.  
v. d. Velden, Münchener medizinische Wochenschrift 1911, p. 184.

Adrenalin injections also deserve consideration in inoperable carcinoma of the root of the tongue. *Echtermeyer* obtained a marked improvement by its use in an advanced case. A proof of the usefulness of this treatment is afforded by the fact that the tumour increased in size whenever the patient left off treatment, in consequence of the improvement which had taken place, and was noticeably reduced in size whenever treatment was resumed. The effect of the adrenalin injections was as follows: Some days after a certain part had been infiltrated several times, a slough was formed, from which dry, white fragments were shed, which occasionally attained the size of a hazel-nut. These very favourable results justify the author in the hope that his method, if applied in good time, will furnish still better results.

Intravenous infusions of adrenalin in very dilute solution, are, according to *E. Holzbach*, very effective in the fall of blood pressure accompanying peritonitis. But as its action is transient, single infusions of adrenalin-saline solutions, especially in advanced cases, may fail. On the other hand, the more concentrated a solution of adrenalin is, the more dangerous it is. But the author's experiments show that continuous infusion of dilute adrenalin-saline solution is effective in keeping up the blood pressure for hours, even in severe cases of peritonitis, and thus time is gained for the removal of the septic poison and for the recovery of the patient.

*Robinson* has used adrenalin (1:1000) internally with very satisfactory results in the vomiting of pregnancy. It may be given in doses of 10 drops. In obstinate cases it may also be injected subcutaneously for a few days. With regard to the theoretical conclusions which the author draws as to the action of adrenalin, his original paper should be consulted.

With regard to the increase in anæsthesia produced by the addition of adrenalin to certain anæsthetics, such as cocaine, alypin, novocaine and tropacocaine, *P. Esch* has made the surprising discovery that even from the point of view of a specific action of adrenalin on nerve tissue, its combination with alypin, novocaine, and especially cocaine, is of great advantage, while a mixture of adrenalin and tropacocaine

*Echtermeyer*, *Berliner klinische Wochenschrift* 1911, p. 1566.

*Holzbach*, *Münchener medizinische Wochenschrift* 1911, p. 1122.

*Robinson*, *Münchener medizinische Wochenschrift* 1911, p. 1535.

*Esch*, *Medizinische Klinik* 1911, p. 1154.

(in the proportion of 5 drops of adrenalin 1:1000 to 100 c. c. of tropacocaine solution) seems useless.

### Airol.

K. Gerson has recently recommended the use of airol in the form of an ointment for both recent and suppurating wounds. The author's experience is that its use in this form guards against bismuth poisoning, such as has been observed after dusting with airol powder (bismuth oxy-iodo-gallate\*). In dealing with recent wounds caused by dirty objects such as cart-wheels, horses' hoofs, and kitchen knives, he did not trouble about special disinfection, but dabbed the wounds a few times with soap spirit and cleansed the parts around the wound with the same solution. Then he applied gauze thickly coated with 5 p. c. airol-vaseline. When the bandages were changed the wound and the surrounding parts were cleansed with benzine. This treatment almost always led to a rapid cure. In ulcers of the leg it was less successful, and in order to stimulate granulation the author added camphor to the airol ointment. (Camphor. 0.5 gramme [ $7\frac{1}{2}$  grains] airol 2.5 grammes [38 grains] vaselin. flav. ad 50.0 grammes [ $1\frac{2}{3}$  oz.].) The results were especially good in recent operation wounds. In these the airol ointment alleviates the pain caused by the wound, prevents the dressings from sticking and hence prevents pain when the bandage is changed, protects the wound from infection and effects a rapid cure.

### Albargin.

This silver-albumose compound, which is distinguished among the newer preparations of silver both for the high proportion of silver (15 p. c.) it contains and for its ready solubility in water, and shares with other related silver compounds the property of not precipitating albumin, is said by G. Seegall to display a reliable bactericidal action on gonococci, and to be relatively slightly irritant. He gave his patients suffering from gonorrhœa injections of an aqueous solution (0.1 to 0.2:200) 3 times a day, with instructions that the solution should be retained in the urethra for 5 minutes. Later

Gerson, *Therapie der Gegenwart* 1910, p. 572.

\*) Compare Merck's Report 1897 and Goldfarb, *Monatshefte für praktische Dermatologie* 1907, No. 5.

Seegall, *Berliner klinische Wochenschrift* 1911, p. 478.

he himself made injections with about 200 grammes of a lukewarm 0.1 p.c. solution of albargin. As a prophylactic, and for abortive treatment he used more concentrated (1 to 5 p.c.) solutions. The results thus obtained were so favourable that albargin was used almost exclusively at the commencement of gonorrhœa and took the place of protargol, which was somewhat relegated to the background. In the author's opinion, albargin is, at the present time, the best remedy for gonorrhœa. It may be used in recent cases as well as in older and chronic cases and on account of its astringent action it frequently brings about a definite cure after the disappearance of the gonococci, without the assistance of astringents. On the other hand, Seegall does not share the opinion that albargin does more to prevent complications than other drugs. He believes the reason for this, apart from mere external considerations, to be in the nature of gonorrhœa, often an obstinate complaint.

### Alcohol.

M. Bockhart has recently again advocated the methodical treatment of eczema by alcohol, particularly in acute and chronic, seborrhœic and non-seborrhœic, but not in weeping or ulcerating eczema. He considers alcohol to be not only a very good antiparasitic, but also to be the only preparation among all the remedies which have been tried for eczema which is under no circumstances harmful. He himself always prescribed it with good, frequently with surprisingly favourable results, using it for destroying the exciters of eczema and their toxins on the diseased skin, and also to prevent complications either in the diseased skin or in the adjoining parts, and finally to guard against recurrences, and as a prophylactic. The author's instructions are to sponge carefully the diseased surface and the adjoining skin twice a day by means of a plug of cotton wool soaked in alcohol (90 p.c.), this is to be done immediately before the application of the drugs used in the treatment of the eczematous tissue (powder, dry painting, ointments, tar, etc.). The application of alcohol has the additional advantage of relieving the itching. The author obtained remarkably favourable results

in the treatment with alcohol of dry eczema in its initial stage; it was also satisfactory in that it warded off post-eczematous furunculosis and pyodermatitis. It is of advantage to continue alcohol disinfection for some time after the eczema is cured.

As is well known, alcohol has of recent years become of much interest as a disinfectant for the skin. According to a communication by A. Zabłudowski, the value of alcohol as a disinfectant is considerably increased by the addition of tannic acid. The author places "alcohol-tannin", a solution of 5 grammes (75 grains) of tannin in 100 grammes (4 oz) of alcohol (95 p.c.), among the best means for the disinfection of the skin. He states that it has not the drawbacks of iodine and iodine-benzine, is much cheaper than alcohol-acetone, acts for a longer period than alcohol by itself, and can be used both for the site of operation and for the hands, while it is said to have no harmful action on the skin. The author's bacteriological experiments show that it is sufficient to treat the hands for 2 minutes, and the site of operation for 1 minute, with alcohol-tannin.

Alcohol appears to be useful in cardiac collapse due to chloroform anæsthesia. As I pointed out last year (Merck's Report 1910, p. 143), inhalations of a mixture of carbonic acid and oxygen have, according to several Italian authors, a good effect in stimulating the automatic action of the respiratory centre during or after chloroform anæsthesia. As recent experiments by Willcox and Collingwood have shown, however, carbonic acid is without influence in heart failure. In these cases inhalations of alcohol vapour and oxygen prove useful, as they effect the rapid return of cardiac activity and raise the blood pressure to its normal level. The method of inhaling is very simple. Oxygen is passed through absolute alcohol and the mixture of alcohol and oxygen thus obtained is conducted to an attachment which is applied to the nose and mouth of the patient. The action is said to take place three minutes after the commencement of inhalation. With the exception of the indication mentioned, the method described is said to render better services than the

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Zabłudowski, Deutsche medizinische Wochenschrift 1911, p. 405.  
Willcox—Collingwood, Klinisch-therapeutische Wochenschrift 1911, p. 651.

inhalation of oxygen alone in pneumonia with weak heart, pleurisy, angina pectoris, asthma, diseases of the myocardium, and valvular lesions.

J. Donath reports on the success of alcohol injections in severe facial neuralgia. In 14 patients, all above middle-age, he injected 2 c. c. of alcohol (90 p. c.), containing 0.005 gramme ( $\frac{1}{12}$  grains) of cocaine hydrochloride in each c. c., and obtained notable results, even in cases in which all other methods of medicinal treatment had failed. In 2 cases the seat of the neuralgia was in the supraorbital and infraorbital nerves, in one case in the infraorbital nerve, in one case in the infraorbital and mental nerves, in 3 cases in the second branch of the trigeminal nerve, and in one case, besides the neuralgia of the supraorbital nerve, there was an empyema of the frontal sinus. At first the injections should be made peripherally, but should this prove unsuccessful, the injections should be made near the foramen ovale or rotundum. L. M. Pussep used for injection into the nerve trunk a solution of 1 gramme of stovaine in 100 c. c. of alcohol (85 p. c.), to which were added 10 drops of tincture of iodine. By using doses of 1 to 3 c. c. no serious complications resulted. After the onset of transitory hyperæsthesia in the region of the injured nerve, after an injection of this kind, complete anæsthesia occurs in the course of 10 to 20 hours. Repeated injections cause the degeneration of the nerve trunk. E. F. Sanz injected alcohol (90 p. c.) in cases of trigeminal neuralgia, and in most cases obtained very satisfactory results. According to H. Braun, alcohol injections render peripheral operations for neuralgia of the second and third branches of the trigeminal nerve practically superfluous, for should a recurrence ensue, nothing stands in the way of a repetition of the injection. On the other hand, an injection is not practicable in the first branch of the trigeminal nerve, at least not near to the base of the skull.

Donath, Budapesti Orvosi Ujsag 1911, No. 25. — Wiener klinische Wochenschrift 1911, p. 1033. — Deutsche Medizinische Zeitung 1911, p. 644.

Pussep, Archiv für Psychiatrie und Nervenkrankheiten 1911, Vol. 48, No. 2.

Sanz, El Siglo medico 1911, 11<sup>th</sup> March.

Braun, Deutsche medizinische Wochenschrift 1911, p. 2414.

### Alcohol, Methyl.

Some years ago\*) I pointed out the danger of using methyl alcohol externally or internally as a substitute for ethyl alcohol. The reality of this danger\*\*) is now fully recognized by experts, and as the necessary steps have been taken by the authorities to stop the substitution of methyl alcohol for ethyl alcohol for medicinal and cosmetic use, it is of interest to be informed of reliable analytical methods for the detection of methyl alcohol, both by itself and mixed with ethyl alcohol. A communication on this subject has been issued by the technical laboratory of the German Imperial Treasury, from which only the method of detecting methyl alcohol shall be quoted here\*\*\*).

The liquid to be tested is distilled in order to increase the proportion of methyl alcohol, and the portion which distils over first is used for the test. 10 c.c. of liquid are distilled until 1 c.c. has gone over. 4 c.c. of 20 p.c. sulphuric acid are added to the distillate and while cooling the mixture, 1 gramme of powdered potassium permanganate is added in small amounts. As soon as the violet coloration of the permanganate has disappeared, the liquid is filtered and gently warmed for a few seconds until it becomes colourless. 1 c.c. of the liquid is mixed with 5 c.c. of concentrated sulphuric acid, being kept cool meanwhile by placing in iced-water, and when thoroughly cold the mixture is added to 2.5 c.c. of a freshly prepared solution of 0.2 gramme of morphine hydrochloride in 10 c.c. of concentrated sulphuric acid. If the liquid to be tested contains methyl alcohol, a violet or dark violet-red coloration will appear either immediately or in the course of at the most 20 minutes, according to the amount of methyl alcohol present\*\*\*\*). If an intense coloration appears at once it proves that the liquid being tested (tincture, fluid extract, mouth wash, liqueur, fruit syrup, etc.) was prepared by the addition of methyl alcohol. In

\*) Compare Merck's Report 1909.

\*\*) Compare Kobert, *Apotheker-Zeitung* 1910, p. 1053. — Lewin, *Apotheker-Zeitung* 1911, p. 54. — *Pharmazeutische Zentrallhalle* 1911, p. 1333.

\*\*\*). Compare *Pharmazeutische Zeitung* 1911, No. 85, p. 860.

\*\*\*\*) Compare Kentmann's reagent for formaldehyde, Merck's *Reagenzien-Verzeichnis* 1908, p. 134 and Marquis' reagent, Merck's *Reagenzien-Verzeichnis* 1908, p. 134.

doubtful cases control experiments are carried out using solutions containing a known amount of methyl alcohol. In the absence of methyl alcohol no violet coloration occurs, the fluid merely becomes cloudy and discoloured on carrying out this test. A very faint coloration, or the appearance of the coloration after the specified time, cannot be considered as a proof of the presence of methyl alcohol.

A. Hellriegel describes a further test. It is based on the demonstration of methyl alcohol by oxalic acid dimethyl ester, which melts at 54°C., and which, in contradistinction to the corresponding ethyl ester, is a crystalline body.

### Allosan.

R. B. Lothian, who has used allosan in several cases of acute gonorrhœa, has expressed the same good opinion as to the value of this preparation as other authors have done before\*). Besides its prompt action on the inflammatory symptoms of the disease, it is almost entirely free from any irritant action on the gastro-intestinal tract. Even though, according to his statement, he obtained a cure in two cases by the daily administration of 15 tablets of 0.5 gramme ( $7\frac{1}{2}$  grains) of allosan without local treatment, yet as a rule it appears better to combine the internal administration of allosan with the usual treatment with injections. In an obstinate case he made use of a solution of potassium permanganate, with which he irrigated the urethra twice a day.

### Almatein.

E. Mazel, in a comprehensive paper, deals with the therapeutic properties of almatein, a condensation product of hæmatoxylin and formaldehyde, in which besides referring to the whole literature regarding almatein, he gives his own experiences.

The author successfully prescribed the drug internally, not only for intestinal dyspepsia and simple and chronic in-

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Hellriegel, *Pharmazeutische Zeitung* 1912, p. 7.

Lothian, *The Therapist* 1911, 14<sup>th</sup> January. — *Nouveaux remèdes* 1911, p. 185.

\*) Compare Merck's Reports 1908 and 1910. — M. Arenstein, *Klinisch-therapeutische Wochenschrift* 1911, p. 1060.

Mazel, *Allgemeine militärärztliche Zeitung*. Reprinted as a supplement to the *Medizinische Klinik* 1910, No. 45.

testinal catarrh, but also for catarrhal jaundice and for diarrhoea occurring during nephritis; his successes, however, were partially due to the suitable hygienic and dietetic treatment recommended by him. It may be pointed out that the curative action of almatein extends from the uppermost part of the small intestine to the rectum. The single dose varies from 0.25 gramme (4 grains) to 1 gramme (15 grains); the daily dose from 1 gramme (15 grains) to 6 grammes (90 grains). For adults the tablet form may be recommended, for little children the following formula is useful: Rp. Almatein 2.5 grammes (38 grains), Sol. Gummi Arabici 25.0 grammes ( $\frac{5}{6}$  oz), Sodii Bicarbon. 0.15 ( $2\frac{1}{2}$  grains), Ol. Cedri 5.0 grammes (90 min.). Sig. A teaspoonful to be taken every 2 hours.

Ertl, who prescribed almatein with good results for painful diarrhoea of pregnancy, combined it in these cases, without unpleasant consequences, with tinct. opii in doses of 15 to 20 drops.

For external use almatein, according to Mazel, is of good service, especially for burns. The fresh blisters are opened with aseptic precautions, the necrotic skin removed, and the entire injured surface is thickly dusted with almatein powder over which a dry dressing is applied. This treatment is also useful for operation wounds and for recent, clean injuries. Infected wounds and incisions in inflammatory processes are better treated in the first place with wet dressings, which have a pronounced analgesic effect. For this purpose the wound is cleansed with benzine, disinfected with corrosive sublimate solution and covered with 10 p.c. almatein gauze. Over this is applied a thicker layer of ordinary, sterile gauze, soaked in distilled water, which should not be too wet. It should be first well wrung out. This is covered with cotton wool freed from fatty matter, a piece of waterproof material and a bandage. Only when the inflammatory symptoms have subsided should the dry dressings again be used. Mazel considers almatein ointment to be more suitable for burns.

Almatein powder, on account of the hæmatoxylin or hæmatein which it contains, is a substance which stains deeply, and must consequently be used with care. Stains on the

\*) This formula is copied from the original paper; whether it corresponds with the author's statements or contains an error, I am unable to say.

Ertl, Heilkunde 1910, No. 4.

hands or linen should be removed with water and a brush, but not with soap, which owing to its alkaline reaction causes the stains to become darker and increases the staining power of the preparation. The discoloured skin surrounding the wound is cleansed with a plug of cotton wool dipped in benzine or dilute acetic acid.

Almatein gauze can be recommended for epistaxis, almatein suppositories for bleeding piles, almatein powder for catarrh of the conjunctiva tunica and phlyctænules, and insufflations of almatein powder for follicular angina.

### Amido-azotoluol.

As I have already pointed out\*), amido-azotoluol in the form of an ointment has frequently proved of value for operation wounds. But the ointment has this disadvantage, that in applying it the healthy skin may easily be covered by it and thus irritation (eczema) is caused. For wound cavities, over which the speedy growth of new skin is desired, it is easy to apply this ointment in too large quantities. In order to avoid this, it is an advantage, according to P. Michaelis, to combine amido-azotoluol with zinc-perhydrol, which in his experience has rendered good service in promoting the growth of skin over large wound surfaces. He prescribes the following powder:

Rp. Amido-azotoluol.	10.0 grammes ( $\frac{1}{3}$ oz)
Zinc-perhydrol.	20.0 grammes ( $\frac{2}{3}$ oz)
Bismuth. subnitr. ad	100.0 grammes ( $3\frac{1}{3}$ oz)

This powder is spread as evenly as possible over the entire surface of the wound, for which purpose he uses an insufflator having several nozzles of different shapes, such as are used in aural practice. A sterile dry dressing is now applied over the wound. The indications for this method of treatment are the same as those for using the ointment. The author points out particularly that the method described is only suitable for clean wounds. For if they are not clean, a copious secretion is produced and the formation of new skin is prevented. Nor should funnel-shaped wounds be treated too soon with amido-azotoluol. The renewal of the dry dressing varies for the different cases, Michaelis never

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\*) Compare Merck's Reports 1909 and 1910.  
Michaelis, Medizinische Klinik 1911, p. 140.

left it for longer than 3 days. If too abundant granulation results, it is cauterised with silver nitrate and then covered with an ointment dressing\*).

### **Ammoniated Citro-Arsenite of Iron.**

This iron preparation is issued by me in the form of green scales, readily soluble in water. It contains 15 to 18 p.c. of iron and 1.4 p.c. of arsenious acid, so that the maximum dose of the preparation is 0.3 gramme (5 grains), and the daily dose 1.0 gramme (15 grains). So far it has been chiefly used in anæmia, malaria, pellagra, and chlorosis. It has been given subcutaneously, but might well be more widely used in therapeutics on account of its valuable properties, particularly as it is well borne. H. Eckhard has recently recommended it for the treatment of the symptoms of chlorosis and anæmia which accompany tuberculosis, for nervous exhaustion and neurasthenia, and further for debility, hysteria, scrofula and other diseases of the lymphatic system. The author found the following treatment to yield satisfactory results: on 3 days in the week 15 divisions of a Pravaz syringe, containing a 5 p.c. filtered solution of the preparation, are injected, but at the first injection only 1 c.c. is given. The injections are given subcutaneously in the region of the chest. A small swelling, slightly painful for about 15 minutes, develops at the site of injection, and soon disappears without affecting the general health. On the whole the injections were well borne, even when continued for a prolonged period, and did not give rise to troublesome by-effects or symptoms; the patients usually got accustomed to them after the second or third injection. Nor did this method of treatment ever cause unpleasant symptoms connected with the stomach or bowel. The success of this iron-arsenic therapy was most evident in the first and second stages of tuberculosis, and was especially apparent in the marked gain in weight of the patients. But in severe cases, also, it was found possible to arrest for a time the progressive loss of strength. Ammoniated citro-arsenite of iron has a stimulating effect on the formation of blood and on metabolism. In every case an increase amounting to at least

\*) Compare also the article on "Azodermin" in this Report. Eckhard, Münchener medizinische Wochenschrift 1911, p. 1186.

10 p.c. in the hæmoglobin content was obtained. In neurasthenic patients the drug diminished the symptoms of irritation, increased the body-weight and also the somatic and psychic capacity for work.

### Ammonium Uranate.

This preparation has already been recommended as an anti-syphilitic\*). This property is confirmed in Mansilla's communication, in which he states that he has obtained very good results in several cases of bilateral neuritis and iritis. Following the method adopted by Weil, the author used a suspension of ammonium uranate in sterile liquid paraffin (5:100) for subcutaneous and intramuscular injections. He injected 1 c.c. (17 min.) of this suspension at intervals of several days, using in all 6 to 7 c.c. (100—120 min.). This treatment by itself brought about the disappearance of the symptoms in the cases of iritis, and caused considerable improvement in the cases of bilateral neuritis. In a case of secondary syphilis, also, the author effected a speedy cure with injections of the drug.

### Amyl Nitrite.

In the treatment of menorrhagia in young girls, F. Hare considers the loss of blood to be due not only to local lesions and changes, but rather to a general constriction of the vessels. To guard against this he tried the nitrites and especially amyl nitrite, as he expected this to have the best action. And indeed this drug proved of value when given in the form of inhalations, for synchronously with the flushing of the face, the menstrual flow diminished or ceased. Still more striking is the fact, observed by the author, that the hæmorrhage arrested in this way does not return until the next period, provided the inhalation takes place not later than during the first or second day of the hæmorrhage. In many cases the inhalation of 3 drops of amyl nitrite sufficed to check the bleeding and to render menstruation normal for the next 3 or 4 periods. If the action of amyl nitrite were found to be temporary, the author also gave nitroglycerin during men-

\*) Compare Merck's Report 1907, p. 25.

Mansilla, *Revista de Medicina y Cirujia practicas* 1911, 28<sup>th</sup> March.  
Weil, *Semaine médicale* 1907, p. 573.

Hare, *British Medical Journal* 1911, 15<sup>th</sup> July, p. 110.

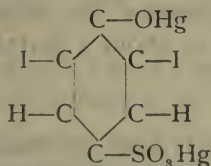
stration with good results. But he states emphatically that the nitrite medication should not lead to the neglect of local conditions.

### Anæsthesine.

Anæsthesine, according to W. Fackelmann, is specially adapted as an anæsthetic for the treatment of wounds, because it never fails nor causes unpleasant by-effects. The author has used it locally in about 4000 separate cases of ulcers of the leg to relieve the pain. After its application in the form of powder or ointment, the patients are immediately or in a short time relieved of pain, and this improvement generally lasts for 2 to 3 days. According to the author's observations, the action of anæsthesine powder in copiously suppurating wounds is more intense than that of anæsthesine ointment, the latter, however, is more suitable in the presence of a slight discharge. A special advantage of employing anæsthesine lies in the fact that the healing process is not delayed by the drug, and that the use of other narcotics, such as morphine, is rendered superfluous. Anæsthesine deserves consideration not only in the treatment of ulcers of the leg by compression, but also in those cases in which the patient is obliged to remain in bed. The numerous cases in which aluminium acetate is not tolerated can be treated with excellent results by anæsthesine and compresses of lead lotion. The satisfactory results which the author has obtained by the use of anæsthesine encourage him to recommend its employment for the treatment of ulcers of the leg.

### Anogon.

This new antisyphilitic is the mercurous salt of iodo-oxy-benzol-para-sulphonic acid (di-iodo-para-phenol-sulphonic acid), of the chemical formula:



It occurs as an extremely fine, sulphur-yellow microcrystalline powder. It contains 48.5 p. c. of mercury and 30.7 p. c.

Fackelmann, Allgemeine medizinische Zentralzeitung 1911, p. 32.

of iodine. It is insoluble in the ordinary solvents. The preparation suspended in oil bears sterilisation at 100° C. without decomposition.

For injection a suspension of 10.25 grammes of anogon in 90 grammes of olive oil is used; in practice a suspension of 1 in 10 should be sufficient. Of this 1 c.c. (one Pravaz syringe-ful) corresponds to 0.048 gramme of mercury.

The first experiments with anogon were carried out by Glaser, and he states that 6 to 8 intramuscular injections of 1 c.c. given at intervals of 5 to 8 days suffice to cause the disappearance of all syphilitic symptoms. But it does not guard against recurrences any more effectively than do other preparations of mercury. The injections were almost always well borne, only a few very sensitive patients complaining of violent pains for a few days. Most of the patients experienced merely a dull sensation or at most a feeling of having received a blow from a stick for a few hours after the injection. Occasionally the author noticed somewhat hard infiltrations at the site of injection, which were slowly absorbed, but he never observed the formation of an abscess. The Wassermann test, which always yielded a positive result at the commencement of treatment, gave a negative result in all the cases tested after treatment with anogon.

E. Terrepson also expresses himself well satisfied with the value of anogon treatment. Like Glaser he considers anogon especially indicated in secondary syphilis; he has not yet tested it in tertiary syphilis. The author draws special attention to the fact that the employment of the preparation causes no digestive troubles and usually no stomatitis; nor does it cause any disturbance of the general health. Anogon proved of such good service in syphilitic phimosis that not a single case in which it was used required operative measures. The symptoms disappeared, on an average, after two injections. In hard chancre the results are equally good and a cure is effected in about a fortnight.

### **Antileprol.**

Antileprol, the ethyl ester of chaulmoogra acid, has the advantage over chaulmoogra oil of being a clear liquid with

Glaser, Deutsche medizinische Wochenschrift 1911, p. 257.

Terrepson, Petersburger medizinische Wochenschrift 1911, p. 152.

a neutral reaction, free from unpleasant taste and smell, and having a low specific gravity. Its administration is facilitated if it is given with wine or with other liquids between meals. At first 10 drops are given daily, 5 drops in the morning and 5 in the afternoon, and the dose is increased by one drop daily. In this way patients are gradually able to take 300 or 350 drops a day, without the occurrence of gastro-intestinal disturbances. F. Barbera treated patients of the working classes in this way, and allowed them to continue with their daily occupation. All improved rapidly. The tubercular nodules diminished in size and the brown and dark blue spots on the skin regained their natural colour. The entire skin, which was tightly stretched, became loose and wrinkled. Besides the internal medication, the author also used the drug subcutaneously; although this was not painful, it did not lead to better results, because the preparation was absorbed too slowly. The resulting swellings caused a tense sensation of the skin, which the author sought to avoid by the addition of 2 or 5 grammes of cycloform to 100 grammes of antileprol, of which he injected single doses of 1 to 2 grammes. The absorption of this mixture was also not satisfactory, and the author now prefers internal administration. He also tried intramuscular injections, but as these cause pain, he does not consider them suitable for ambulatory practice. On the whole Barbera expresses himself well satisfied with the results of antileprol treatment.

Engel-Bey believes he has found in antileprol the means of curing leprosy. But it should be used for at least 1 to 2 years. He suggests as a daily dose 2 to 5 grammes, which should be taken in warm tea or warm milk during meals. The drug may also be given in gelatin capsules. If digestive disturbances or fever ensue, the medicine should not be discontinued, but the dose should be reduced for a short time.

### Antimeristem.

In 1904 and 1905 O. Schmidt published his first reports dealing with a parasite occurring in malignant tumours, of

Barbera, Extract from a paper read at the III<sup>rd</sup> Spanish Congress for Oto-Rhino-Laryngology at Seville in April, 1910, (Reprint.) Engel-Bey, Therapeutic Medicine 1911, January. Compare Merck's Report 1909, p. 110.

Schmidt, Monatsschrift für Geburtshilfe und Gynäkologie Vol. 17, Supplementary number. — Münchener medizinische Wochen-

which no pure cultures could be prepared without the aid of an intermediate host, for which the author used *mucor racemosus*. His statements have, as far as I know, not been accepted in scientific or zoological quarters; but cancer lymph, called originally "cancroidin Schmidt", and later "antimeristem", and prepared on the basis of Schmidt's results, has aroused the interest of various doctors, among whom are several authorities on cancer research and the treatment of cancer. On account of the hopeless prospects in the treatment of inoperable cases of carcinoma and sarcoma, interest in the drug has also been awakened in lay circles, for, according to Schmidt, this preparation offers the only specific means of effecting a cure. The preparation will therefore be referred to here as briefly as possible; it represents a sterile extract of a *mucor* culture infected by Schmidt's parasite, i. e., a pure culture of the above mentioned parasite grown on *mucor*\*).

As is usually the case with new remedies, very satisfactory results were obtained with antimeristem (cancroidin) by several doctors; but ere long failures were recorded by authorities, so that the value of the preparation was questioned. Schmidt himself reported upon the early successes. Then Aronsohn reported a case of carcinoma of the larynx, Jenssen a case of cancer of the tongue, Neander a case of carcinoma of the rectum, Schulhoff a case of carcinoma of the breast, Claes a case of sarcoma of the jaw, de Beule recorded several cases treated by other authors, Michele reported a case of uterine cancer and Crolla a case of

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schrift 1906, No. 4. — Deutsche medizinische Wochenschrift 1908, No. 7 and 11. — Wiener medizinische Wochenschrift 1908, No. 27 and 28. — Zentralblatt für Bakteriologie 1908, No. 3 and 1909, No. 1. — Communication from Dr. Schmidt's Laboratory for cancer research, Book 1 and 2. Published by Martin Hager in Bonn.

\*) Compare Baisch, Deutsche medizinische Wochenschrift 1908, No. 7.

Aronsohn, Zeitschrift für Krebsforschung Vol. 9, p. 367.

Jenssen, Deutsche medizinische Wochenschrift 1910, No. 16.

Neander, Deutsche medizinische Wochenschrift 1908, No. 5.

Schulhoff, Gyogyaszat 1909, No. 43, p. 717.

Claes, Presse médicale belge 1908, No. 42.

de Beule, Geneeskundige Tijdschrift vor Belgie 1910, No. 12 and 13. — Belgique Médicale 1910, No. 48 and 49.

Michele and Crolla, from a prospectus of the Bacteriological and Chemical Laboratory of W. Schmidt in Cologne.

sarcoma, in some of which antimeristem is said to have rendered excellent services. In opposition to these are Czerny's experiences; he treated a number of cancer patients with antimeristem without achieving a single cure. He states that subjective improvement was only observed in a third of the cases. Nor could Winkler, Küll, Nosek, Ewald and Burckhardt ward off the fatal termination in cancer cases treated by them with antimeristem. Sick used antimeristem in five cases of inoperable carcinoma, all definitely diagnosed as cancer, long enough to enable him to form an adverse opinion, for the objective improvement was always transitory, and the use of more concentrated preparations was very painful. Nor does Hauser, as a result of his experiences, regard antimeristem as an efficacious remedy for cancer. Beresnegowsky and Kolb, who had no better success, examined the tumours pathologically after their failures and found that the treatment by antimeristem had neither arrested the growth of the carcinoma, nor had it hindered the formation of metastases.

Thus successes and failures are diametrically opposed, and it would be very difficult to express a decided opinion. If we consider the experiences of such an authority as Czerny, we incline to the view that those cases said to have been cured by this means were probably not true carcinomata; this would not be extraordinary, considering the difficulty in the diagnosis. A good illustration of the possibility of making an error is given by Kolb, who found a tumour of the rectum, the size of a goose's egg, in a patient who had 4 months previously undergone an operation for cancer; this he took to be a recurrence of the carcinoma. In two months the tumour had completely disappeared. Kolb correctly remarks: "Had we on first seeing the patient started treatment with antimeristem, we should have believed that we had achieved a remarkable cure by this means".

Czerny, Zentralblatt für Chirurgie 1910, No. 31.

Winkler, Medizinische Klinik 1909, No. 44.

Küll, Medizinische Klinik 1910, No. 36.

Nosek, Wiener klinische Rundschau 1911, No. 48.

Ewald and Burckhardt, communicated by Kolb.

Sick, Münchener medizinische Wochenschrift 1911, No. 23.

Hauser, Medizinische Klinik 1911, p. 1389.

Beresnegowsky, Zeitschrift für Krebsforschung Vol. 9, p. 373.

Kolb, Münchener medizinische Wochenschrift 1911, No. 20.

To judge by past experiences it is impossible at present to express a definite opinion as to the value or the uselessness of antimeristem in the treatment of inoperable carcinomata.

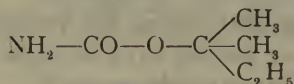
As regards the dosage and method of using Schmidt's lymph, reference should be made to the instructions accompanying the preparation.

### Aperitol.

In cases of constipation it is often necessary to vary the drugs, as the same aperient is either not tolerated, or the patient may become accustomed to it. According to W. Lustwerk, aperitol deserves full consideration as a remedy fulfilling all the requirements which may be reasonably demanded from a laxative, for it is harmless, causes no pain nor by-effects and acts promptly. It is indicated in all cases in which a purgative is required for a considerable period, as the patient is said not to grow accustomed to it even after prolonged use. The author states that a special advantage of aperitol over other laxatives is that the dose can be gradually reduced without diminishing its action. Many patients continue to have a regular action of the bowels for a long time after leaving off the drug. Aperitol may be prescribed with advantage for patients who are unable to stand stronger purgatives, e. g., in nephritis, and in those cases in which the condition of the gastro-intestinal mucous membrane demands careful treatment. With regard to the dosage of aperitol, this has been given in former Reports\*).

### Aponal.

The carbamic acid ester of tertiary amyl alcohol, that is the amylene carbamate of the chemical formula



is issued under the name of aponal. Like hedonal,  $\text{NH}_2\text{—CO—O—CH(CH}_3\text{)C}_3\text{H}_7$ , with which it is chemically closely related, aponal is used therapeutically as a hypnotic. O. Huber carried out the first pharmacological experiments with this preparation. They proved that the hypnotic action of aponal

Lustwerk, Petersburgers medizinische Wochenschrift 1911, p. 443.

\*) Merck's Reports 1908—1910.

Huber, Medizinische Klinik 1911, p. 1236.

is very similar to that of amylene hydrate, only it sets in slightly later than is the case with the latter. This property no doubt depends upon its insolubility in water, in consequence of which aponal is more slowly absorbed. The lethal dose for a cat is the same as that of amylene hydrate. The author has never observed the occurrence of severe symptoms of intoxication or excitement in experiments on animals.

In experiments on man, aponal, according to Huber, has proved a useful hypnotic in mild cases of agrypnia. It acts within 20 to 30 minutes and produces light, peaceful sleep, which is not so deep as the slumber produced by veronal. It has neither an analgesic nor a sedative action. It is therefore indicated in cases of insomnia consequent upon nervousness, over-fatigue, excitement, etc. No prolonged effect was observed after waking, nor any secondary action on the stomach, intestine or other organs. The hypnotic dose of aponal is 1 to 2 grammes (15—30 grains). In the author's experience, a larger dose is not advisable, as it may call forth delirious symptoms. In a patient who had in one night been given first 2 grammes (30 grains), and then 1 gramme (15 grains), Huber observed a state of mental confusion on rising in the morning. The author considers a combination of this preparation with the more powerful acting veronal to be specially called for in cases in which veronal takes some time to act. Aponal would cause drowsiness and thus introduce the action of veronal.

### Arsacetin.

The communications of J. Morgenroth and L. Halberstädter are of great interest for the therapeutic treatment of trypanosomiasis. These authors relate their experiences with regard to the resisting power of the trypanosomes to arsacetin and several other drugs commonly used in the treatment of this disease. For details of their experiments their original paper should be consulted; a summary of their conclusions only will be given here. "The exclusive use of arsacetin yields a Nagana strain, which possesses the maximum resisting power to arsacetin. — At the same time this strain has also attained the maximum resistance to tartar emetic. — This strain exhibits a high degree of resistance,

Morgenroth-Halberstädter, *Archiv für Schiffs- und Tropen-Hygiene* 1911, Vol. XV.

though not absolute, to dioxy-diamido-arsenobenzol, and a relatively low resistance to arsenophenylglycin. — When the treatment by arsacetin is left off, the resistance to antimony is lost, whereas the resistance to arsacetin is not noticeably altered. — By a single treatment with tartar emetic, but not by many weeks' treatment with arsacetin, resistance to antimony is once more regained."

### **Arsenferratose.**

The administration of arsenferratose\*) at the same time as sodium bromide in epilepsy accompanied by severe secondary anæmia has proved a most useful measure. P. Joedicke prescribed it for his patients in doses of a tablespoonful 3 times a day after meals, and controlled the results by blood examinations. At the end of a few weeks he was able to confirm in numerous cases that the hæmoglobin content of the blood had increased. The patients gained in weight, the appetite increased and the general condition improved. The improvement in the physical condition was accompanied by an increased power of resistance to epileptic fits; the author was able during the experimental period to observe a decrease in the number of fits as well as a diminution in their severity. The bromide acne, due to the employment of sodium bromide, was favourably influenced by arsenferratose. The author specially points out that the preparation is not injurious to the teeth, and does not derange the stomach or bowel, even in persons subject to intestinal trouble.

Arsenferratose is also favourably dealt with in a report by C. A. Crispoli, of the medical clinic of Rome. He states that the preparation was used with success in chlorosis and chloro-anæmia, and in secondary anæmias due to various causes (arterio-sclerosis, neurasthenia, epilepsy, cardiac neurosis, pneumonia, syphilis, influenza, hysteria, etc.). In order to obtain a satisfactory result, the prolonged use of the medicine is indicated, for the improvement only becomes manifest in a fortnight. In severe cases the author at first kept the patient in bed and later forbade all mental and physical exertion and ordered a suitable diet. The dosage was as follows: at first

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\*) Compare Merck's Report 1907.

Joedicke, Psychiatrisch-neurologische Wochenschrift Vol. 12, No. 35. — Wiener klinische Rundschau 1911, p. 65 and 338.

Crispoli and Marinacci, Clinica medica italiana 1911, No. 3.

a small teaspoonful was given 3 times a day after meals, gradually increasing the dose until a tablespoonful was taken. According to the severity of the case the treatment lasted from 15 days to 3 months. The maximum action occurs in 2 to 3 weeks. Arsenferratoze was always readily taken, and was well borne. P. Barbier also obtained very satisfactory results in chlorosis and anæmia from the use of arsenferratoze.

E. A. Tavonius used arsenferratoze as a roborant in tertiary syphilis in conjunction with mercurial treatment, and had very satisfactory results. The author specially recommends that those cases of syphilis which do not respond to potassium iodide should be treated with arsenferratoze. The preparation is, in his experience, well borne, readily taken, does not cause constipation, and does not affect the teeth.

### **Arsenophenylglycin.**

Scherschmidt reports on the use of arsenophenylglycin\*) in the treatment of sleeping sickness in East Africa. Small doses (0.5 gramme) [ $7\frac{1}{2}$  grains], such as are adequate when atoxyl is used, do not suffice in the case of arsenophenylglycin. In adults 1.5 grammes (24 grains) were injected on 2 consecutive days and sometimes a single dose of 2 grammes (30 grains) was given. Children were usually given two doses of 0.75 gramme (12 grains). The injection (of the 10 p. c. solution) was usually made into the skin between the shoulder-blades. The formation of an abscess was only observed once, but usually swellings formed which affected the general health; the patients also complained of abdominal pain. Some complained of itching of the skin, others of a rash, which disappeared in a few days.

From the statistics supplied by the author it is seen that recurrent cases, which had been successfully treated with atoxyl, and in which the trypanosomes had become tolerant to atoxyl, were not noticeably influenced by treatment with arsenophenylglycin. In 25 patients who had not been previously treated and the greater part of whom were suffering from a mild attack, the condition of one patient remained unchanged, 3 were improved in so far as the swollen glands

Barbier, *Courrier médical* 1911, No. 44.

Tavonius, *Wratschebnaja Gaceta* 1911, No. 2.

Scherschmidt, *Deutsche medizinische Wochenschrift* 1911, p. 292.

\*) Compare Merck's Reports 1909 and 1910.

disappeared and during the time of observation showed no trypanosomes; in 6 patients the trypanosomes reappeared in the blood sooner or later. In 5 the condition grew worse without fresh trypanosomes being found — i. e., symptoms of sleeping sickness appeared — and in 11 cases (including 8 with a mild attack) a fatal termination could not be prevented. Scherschmidt considers these discouraging results of arsenophenylglycin treatment to be due to the poisonous properties of the drug and the use of too large doses, although these were not as large as were recommended by Ehrlich. In spite of the toxicity of the doses administered, the parasites were not wholly eliminated nor yet totally destroyed. As an increase in the dosage appears dangerous, and as the doses mentioned are too poisonous and smaller amounts would prove useless, the conclusion arrived at by the author, that arsenophenylglycin is not destined to fulfil the hopes set upon it, is probably correct. Nor does Scherschmidt expect a better result from the combination of arsenophenylglycin with aniline dyes. It is of interest to note that he made the observation that atoxyl displayed a favourable action after arsenophenylglycin had failed. Therefore a variation in arsenic medication would appear to be of advantage in sleeping sickness.

### Arsentripherol.

K. Thomas recommends the use of arsentripherol for the arsenic and iron treatment of neurasthenia, hysteria, scrofula, rickets, severe loss of blood (post-partum, in menorrhagia, myomata, retroflexion of the uterus, at puberty), in convalescence from prolonged fever and constitutional diseases (lead poisoning, diabetes, tapeworm, syphilis), in anæmia and general debility\*). For adults, 3 tablespoonfuls a day may be prescribed, for children, according to their age, from a teaspoonful to a dessertspoonful. The drug is pleasant to take and does not incommode the stomach or the digestion. Its action is apparent in the resulting improvement in the general condition, in the appetite, and in digestion. It is also said to occasion spontaneous stools. In scrofula and rickets it renders good services indirectly by improving the general strength. Enlarged glands and eczema are cured by the use of arsentripherol

Thomas, Medizinische Klinik 1911, p. 818.

\*) Compare Merck's Report 1908.

accompanied by local treatment, as the quality of the blood is distinctly improved by the preparation.

### Asphalt.

Two years ago H. Floer commented on the advantages of asphalt fumigations in the treatment of pulmonary tuberculosis. He drew special attention to its favourable influence on the expectoration, the general health and the appetite. These experiences are confirmed in Pick's communications, who particularly noticed a great improvement in the appetite as a consequence of this treatment. In some cases of pulmonary catarrh and bronchitis, the author already in the first week after commencement of the asphalt treatment found that the patient had gained in weight without any other internal remedies having been used. In his opinion the asphalt inhalations act as a powerful stimulant on the gastric mucous membrane and thus improve the appetite. The inhalations are said not to be unpleasant, and do not irritate the mucous membrane of the throat or of the respiratory tract, even after the patient has spent an hour in the inhalation chamber. Expectoration is at first increased, but in a short time it becomes less and may disappear entirely. In many cases the night sweats were also found to diminish. As a result of the treatment, the general condition of the patients was so much improved that they felt considerably relieved, were able to continue their work, or if they had not been able to work, they could return to their professional duties after a course of inhalations extending over several weeks. Besides the asphalt inhalations, Pick also made use of Kuhn's suction mask, which he applied for 15 to 20 minutes daily. The author considers that the expansion of the chest which was obtained was due to this measure. For the asphalt fumigations he used fumiform or eufuman.

### Aspirin.

W. Ebstein has suggested a new indication for aspirin. By chance he discovered that this drug, used for so many purposes, was also of decided benefit in coughs. In his ex-

Floer, *Therapie der Gegenwart* 1909, p. 405. — Merck's Report 1909, p. 214. (Compare also Weber, *Ärztliche Vierteljahrs-rundschau* 1910, April.)

Pick, *Allgemeine medizinische Zentral-Zeitung* 1911, p. 368.

Ebstein, *Deutsche medizinische Wochenschrift* 1911, p. 1476.

periments he found that it not only caused a transitory improvement, like the narcotics, but that it brought about an actual cure and shortened the duration of the illness. Compared with narcotic drugs, it is harmless, so that further tests in this direction would be of interest. In a case of pulmonary emphysema with increasing cardiac weakness in a woman aged 74, the author gave 4 doses of 0.5 gramme ( $7\frac{1}{2}$  grains) of aspirin within 24 hours. The fits of coughing were considerably shortened, the expectoration decreased, and the catarrh was cut short so that it completely disappeared in a week. The success obtained in this case is especially noteworthy, because the patient had for years suffered from attacks of coughing dragging on for weeks.

Further communications with regard to aspirin have been published by J. Biro, Graham, Klingberg, Bondi and Katz. Graham reports a case of idiosyncrasy to aspirin, in which after 2 doses of 0.3 gramme (5 grains) severe symptoms of poisoning occurred within an hour; cardiac weakness and œdematous swellings of the face and mucous membranes occurred, and these symptoms only disappeared slowly in the course of several days. Klinger also observed similar symptoms after a dose of 0.5 gramme ( $7\frac{1}{2}$  grains) of aspirin. Gastric discomfort and heartburn are said to occur frequently after aspirin medication, but Biro is of opinion that the by-effects produced by the preparation are unimportant and may be neglected, for these occur with every drug. He considers it one of the very best antirheumatics, which also renders good service as an antipyretic and an antineuralgic. In typhoid fever the antipyretic action of aspirin, according to Bondi, is evident even with small doses of 0.25 gramme (4 grains), whereas the other derivatives of salicylic acid do not display this effect, at any rate not when given in such small doses. For this reason the preparation would be of particular interest in the treatment of typhoid fever. Bondi and Katz also found that it exhibited a powerful antipyretic action in heat stroke, such as is not produced by salicylic acid. They therefore include acetyl-salicylic acid in the class of fever narcotics.

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Biro, Zentralblatt für die gesamte Therapie 1911, p. 267.

Graham, Journal of the American Medical Association 1911, January 28.

Klingberg, Zeitschrift für Veterinärkunde 1911, p. 365.

Bondi-Katz, Zeitschrift für klinische Medizin Vol. 72, No. 2.

**Asurol.**

The treatment of syphilis\*) with asurol, according to Th. Mayer, offers the advantage of enabling comparatively large doses of mercury to be introduced into the system in an unobtrusive manner and without causing appreciable disturbances. After the addition of 1.5 p.c. of alypin nitrate, injections of a 5 p.c. or 10 p.c. asurol solution are said to be well borne. In carrying out an energetic cure, the author gave 12 injections of 2 c.c. (34 min.) of a 10 p.c. solution (2 injections a week), thus using altogether 2.4 grammes (36 grains) of asurol, and by this means the action was quickly displayed. M. Kunreuther injected 2 c.c. (34 min.) of a 5 p.c. solution of asurol on alternate days, and in almost every case obtained a beneficial effect on the syphilitic symptoms, which disappeared with comparative rapidity, while by-effects were only observed in exceptional cases. The latter probably depend upon the individual sensitiveness of the diseased part, for in one case, after each injection into the gluteal region, the author observed the appearance of red, cedematous swellings, the size of the palm of the hand. But it never affected the kidneys and only rarely gave rise to stomatitis. Recurrences occurred in the same way with asurol treatment as when mercury salicylate was used, more especially if the injections were discontinued immediately the syphilitic symptoms disappeared. In tertiary syphilis the action of asurol does not appear to equal that of calomel. In Kunst's experience, it is not superior to mercury salicylate in its action, and is inferior to the latter in local and general effects. The author only concedes one advantage to asurol, viz., that as a soluble compound of mercury it does not carry with it the danger of embolism. But as this can be avoided in practically every case with a slight amount of skill and with practice, he has given up the employment of asurol. Welander considers the combination of asurol and grey oil to form a good and energetic method of treatment, even

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\*) Compare Merck's Report 1910.

Mayer, Berliner klinische Wochenschrift 1911, p. 529.

Kunreuther, Monatshefte für praktische Dermatologie 1911, Vol. 52, p. 234.

Kunst, Klinisch-therapeutische Wochenschrift 1911, p. 163.

Welander, Nordisches medizinisches Archiv 1911, Vol. 44, Part II, p. 2.

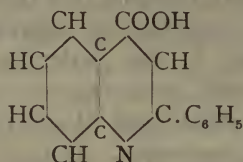
though, in his opinion, it is not superior to the use of mercury salicylate and oleum mercurioli.

In investigating the bactericidal action of asurol on the eye of a rabbit, L. Schreiber came to the conclusion that instillations of asurol solution and inunction with asurol ointment had no antiseptic action on an experimentally produced corneal ulcer. The use of very concentrated asurol lotions (over 2.5 p.c.) appears to arrest the inflammatory process, but at the same time causes fatal intoxication. Even though the amount of asurol used in this manner in man would not have had a lethal result, still more or less mild toxic symptoms would probably be present. In the application of asurol in the form of subconjunctival injections, the corneal ulcer was cured in two cases, while in 12 cases it failed, so that no great weight can be attached to the few positive results.

### Atophan.

After Nicolaier and Dohrn had shown that the quinolin-carbonic acids and especially 2-phenyl-quinolin-4-carbonic acid, are able to produce a great increase in the excretion of uric acid, therapeutic interest was aroused in the last named acid. It is now issued under the name of atophan, in the form of a crystalline product, insoluble in water.

Atophan melts at 208°—209° C., and has the following chemical formula:



E. A. Tschernikow and J. S. Magat employed atophan (phenylcinchoninic acid) in several cases of arthritis urtica and articular rheumatism, and observed an increase in the

Schreiber, von Graefes Archiv für Ophthalmologie 1911, Vol. 78, No. 2.

Nicolaier-Dohrn, Deutsches Archiv für klinische Medizin 1908, p. 331. Compare also: Starkenstein, Archiv für experimentelle Pathologie 1911, Vol. 65, p. 177 and 196. — Frank and Bauch, Berliner klinische Wochenschrift 1911, p. 1463.

Tschernikow-Magat, Charkomski Medizinskij Journal 1910. — Zentralblatt für innere Medizin 1911, p. 139.

excretion of uric acid in all their patients, whether they were restricting themselves to a purin-free diet, or not. Occasionally also an increase in diuresis was observed. The success of atophan treatment was not only apparent in gout, but also in uric acid diathesis, in acute articular rheumatism and in the exacerbations of the latter. In chronic rheumatism, on the other hand, the success was not marked. The increase in the elimination of uric acid after the use of atophan is so great, that, according to W. Weintraud's experience, there is danger of the appearance of renal colic in those suffering from gout. For this reason care should be taken to eliminate the uric acid from the system in a soluble form. To ensure this the patient should be encouraged to drink plenty of fluid and to take 5 to 10 grammes (75—150 grains) of sodium bicarbonate daily. By this means the urine, which has become acid by the administration of atophan, is rendered alkaline and the excretion of uric acid in a crystalline form is prevented. It is always advisable to keep a careful watch on the patient's urine while atophan is being administered. Further, the author insists that besides the administration of atophan the physical methods of treatment, exercises, thermal baths, mineral waters and diet, especially abstention from alcohol, should not be neglected.

F. Deutsch also expresses himself well satisfied with the action of atophan in acute gout. His experience, however, is that in chronic gout the action is less favourable. Atophan was as a rule well borne, and only occasionally were unpleasant by-effects observed, such as abdominal pain, acid eructations and diarrhoea, which were, however, eliminated by the administration of small doses of sodium bicarbonate.

Georgiewski, also, in most cases achieved subjective and objective improvement in the arthritic symptoms by the use of atophan. This improvement, however, depends upon the continued use of the drug, for if it be discontinued the symptoms reappear. On the other hand, the author in no case observed unpleasant by-effects, even when the preparation was given on 10 consecutive days.

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Weintraud, *Therapie der Gegenwart* 1911, p. 97.

Deutsch, *Münchener medizinische Wochenschrift* 1911, p. 2652.

Georgiewski, *Deutsche medizinische Wochenschrift* 1911, p. 1030.

E. Heller, who made a special study of the use of atophan in articular rheumatism, came to the same conclusions as Tschernikow. It acted well in acute articular rheumatism, but usually failed in the chronic form, in which the treatment with drugs always encounters difficulties.

Atophan is prescribed in doses of 1 gramme (15 grains) to be taken 3 times a day, or in doses of 0.5 gramme ( $7\frac{1}{2}$  grains) 4 times a day.

With regard to the action of atophan on purin-metabolism, reference may be made to the publications of Starkenstein, Fromherz, Frank and Bauch.

G. Zuelzer regards atophan as a diagnostic and advances the following hypothesis: As a rule, the administration of atophan enables a diagnostic differentiation to be made between gout and all articular affections not due to gout; in the former a considerable amount of excretion of uric acid in the urine takes place for a prolonged period, at least until the joint trouble has been relieved, while in the articular affections not due to gout the uric acid excretion is slight and does not continue beyond the first or second day.

### Atoxyl.

In the treatment of sleeping sickness, atoxyl is apparently holding its own, notwithstanding the competitive preparations which have been produced in recent years. This is apparent in the communication of Scherschmidt. According to Ullrich, arsacetin and arsenophenylglycin are not superior to atoxyl, for although both drugs, like atoxyl, possess an effective trypanocidal effect, their use entails a great danger of intoxication. Ullrich, therefore, prefers atoxyl. He now administers it in such a way that the patients are given a double injection of 0.4 to 0.5 gramme ( $6-7\frac{1}{2}$  grains) at intervals of 10 to 14 days, altogether receiving 10 to 12 double injections, followed by a pause of about 3 months. This method is said to have the great advantage that the visual disturbances, which have been observed to follow the administration of atoxyl, appear less frequently than was formerly the case. In

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Heller, Berliner klinische Wochenschrift 1911, p. 526.

Fromherz, Biochemische Zeitschrift 1911, Vol. 35, p. 494.

Zuelzer, Berliner klinische Wochenschrift 1911, p. 2101.

Scherschmidt, Compare the article on Arsenophenylglycin.

Ullrich, Archiv für Schiffs- und Tropenhygiene 1911, No. 2.

treating nearly 800 patients (mostly in the first stage) the author achieved a complete cure in 25 p. c. of the cases. As he has seen recurrences 15 months after completion of the treatment, he does not regard a case as cured unless 2 years after treatment the patient is feeling perfectly well and the blood is free from trypanosomes.

The question as to how atoxyl acts has been taken up by several authors. Thus Ehrlich considers the action of the drug to be due to reduction products formed in the system, Levaditi and Yamanouchi seek the action of atoxyl in its combinations with the body albumins, Blumenthal believes the arsenic which is split off in the system to be the active agent, and finally it is conceivable that atoxyl assists in the production of antibodies. So, however, was able to prove experimentally that atoxyl has no influence on the production of antibodies.

B. Knothe, who reports on the use of atoxyl in the treatment of tuberculosis, used it in altogether 18 cases. His results show that the preparation has a curative effect, even in the last stage of the disease. The author even believes that the drug may have a certain specific, bactericidal action on the tubercle bacilli in the organism. His method of treatment consisted in the administration of a series of atoxyl injections. The doses, given daily or at intervals of a few days, generally varied between 0.3 and 0.5 gramme (5—7½ grains).

An experiment of interest to veterinary medicine is the test of the value of atoxyl in the treatment of foot-and-mouth disease in cattle. According to L. Mayr, the preparation exhibits no prophylactic action against the causative organism of this disease, but animals which have been treated with the drug beforehand are not attacked so severely. They do not lose their appetite and are spared from complications such as abortion and emaciation. The curative action of atoxyl is of great importance, for, in the author's experience, it considerably curtails the course of the disease. Certainly the timely injection of atoxyl, due attention being paid to correct dosage, individuality of the animal, its age, sex and body weight, is fairly effective in preventing cases of death. An injection of atoxyl is given on the first day on which

So, Wiener klinische Wochenschrift 1911, p. 452.

Knothe, Wiener klinische Wochenschrift 1911, p. 562.

Mayr, Berliner tierärztliche Wochenschrift 1911, No. 47—49.

the disease has been diagnosed and, according to the severity of the case, is repeated several times at intervals of 1 to 2 days. The single dose for large animals, such as bulls, draught-oxen, fattened animals and heavy pregnant cows is, according to their body weight, up to 4 grammes (60 grains) of atoxyl, for young cattle, 2.25 grammes (34 grains), for calves and goats, 1.25 grammes (20 grains). A 15 p.c. aqueous, sterile solution is used for the injections.

### Atoxylate of Mercury.

Several experiments with the use of injections of atoxylate of mercury\*) in syphilis were carried out by E. Welander and showed that atoxylate of mercury is a useful drug, even though it does not in every case lead to the desired result. In one case of sclerosis without general symptoms, the latter did appear, but they soon disappeared again. In a severe case of sclerosis with papular syphilide and syphilis of the veins, the symptoms improved without, however, totally disappearing. In three cases of secondary syphilis, the symptoms which were present disappeared, but in one case prolonged treatment was just as ineffective in preventing a recurrence as was a mercury cure, using oleum mercurioli. In pustular syphilides, also, injections of atoxylate of mercury were followed by cures as well as by recurrences, but in these cases salvarsan gave no better results. Gummatous swellings healed rapidly. With regard to the by-effects of the injections, in a few cases they were followed by large, painful infiltrations, in two cases the author observed stomatitis and in one case disturbance of vision, but in no case did they give rise to any severe eye complaint. On the whole, Welander's communication has shown that atoxylate of mercury undoubtedly acted on the syphilitic symptoms.

### Atoxylate of Silver.

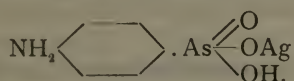
Atoxylate of silver, (atoxylic silver or argenti atoxylas) was first tested pharmacologically by F. Blumenthal, who

\*) Compare Merck's Reports 1908—1910.

Welander, Nordisches medizinisches Archiv 1911, Vol. 44, Part II, p. 6.

Blumenthal, Biochemische Zeitschrift 1910, Vol. 28, p. 91. — Deutsche medizinische Wochenschrift 1910, p. 2275. — Therapie der Gegenwart 1911, p. 388.

showed that it was not more toxic than atoxyl. The preparation is insoluble in water, and the chemical formula for this mono-silver salt of para-amino-phenylarsonic acid is:



According to Blumenthal, atoxylate of silver contains 23 p.c. of arsenic and 33 p.c. of silver. The high percentage of silver it contains seemed to justify the assumption that the drug would prove serviceable in gonorrhœal and septic processes. As it can be injected subcutaneously without giving rise to by-effects Blumenthal considered it specially suitable for the treatment of gonorrhœal arthritis. J. Hirsch next tested the use of this new silver preparation in puerperal infections, and his results confirmed its utility in septic affections. The drug saved life in a desperate case of bacteræmia, in which probably both the silver and the arsenic components of the preparation exerted their action. H. Eisenberg, who published a detailed account of this case, gives the following formula for the use of atoxylate of silver:

Rp. Atoxylate of silver                    1.0 gramme (15 grains)

Ol. oliv.                                        10.0 grammes (1/3 oz)

M. Ft. emuls. Sig.: 3 to 4 c.c. (50—70 min.) to be injected intramuscularly at intervals of 24 to 48 hours.

As may be gathered from the communications of Hirsch and Eisenberg severe infiltrations may be expected to occur at the site of the injection of atoxylate of silver.

### Atropine Methylbromide.

As I already reported\*), Tabora pronounced atropine sulphate a valuable drug for the treatment of gastric ulcer; it rapidly causes the disappearance of pain and brings the stomach to rest. According to G. Singer, atropine methylbromide is equally useful in these cases. He found that the following prescription had a most favourable influence on the hypersecretion and hyperacidity, as well as on the accompanying pains:

Hirsch, Medizinische Klinik 1911, p. 1084.

Eisenberg, Berliner klinische Wochenschrift 1911, p. 1643.

\*) Merck's Report 1908, p. 143.

Tabora, Münchener medizinische Wochenschrift 1903, p. 1992.

Singer, Medizinische Klinik 1910, p. 2009.

Rp. Atropin. methylbrom. 0.005 gramme ( $\frac{1}{12}$  grain)

Aq. aurant. flor. s. dest. 100.0 grammes ( $3\frac{1}{3}$  oz)

Sig.: A dessertspoonful to be taken 2 to 3 times daily.

### Aurochin.

Aurochin, the para-aminobenzoic acid ester of quinine, belongs to the quinine esters which have only a slightly bitter taste. The preparation is relatively sparingly soluble in water, but can be dissolved by boiling with 10 times the amount of water. The resulting solution has, however, a bitter taste. This circumstance is of no consequence in the parenteral employment of aurochin, as was suggested by A. Plehn. For this purpose a freshly prepared, aqueous solution of aurochin (1:10—15), which has been boiled and thereby sterilised, is used. This is injected into the buttocks, and is probably also suitable for rectal application, as the experiences of the author have so far shown it to be non-irritant. If the internal administration is not suitable on account of vomiting, and the intra-gluteal application cannot be carried out in the absence of the physician, it should be possible for the nursing staff to apply the drug by the rectum. The indications for aurochin are the same as those for quinine. The dose may be fixed as being one quarter larger than that of quinine.

### Azodermin.

In employing amido-azo-toluol in the form of an 8 p.c. ointment, Gurb ski observed symptoms resembling anilin poisoning in the case of a child aged 11, which was suffering from an extensive burn on the thigh; this was most probably due to the application of the preparation to a relatively large area of skin. In order to avoid occurrences of this nature, F. Curschmann experimented with an amido-azo-toluol, the amido-group of which was acetylated, so-called azodermin. This preparation is a yellowish-red powder, less readily soluble in alcohol and ether than amido-azo-toluol. Its staining power is weaker than that of scarlet red. Curschmann was able to prove, in experiments on animals, that azodermin appears non-toxic as compared with amido-azo-toluol, so that there is no objection to its clinical use. He used it in the form of

Plehn, Therapie der Gegenwart 1911, No. 12.

Gurb ski, Zentralblatt für Chirurgie 1910, p. 1550.

Curschmann, Therapeutische Monatshefte 1911, p. 717.

an 8 p.c. ointment in 200 cases of wounds, ulcers of the leg, burns, and badly healing granulations; especially in wounds caused by burns his results were remarkably good. After removing the blisters, the wound surfaces were covered with the azodermin ointment. There was scarcely any discharge, and the wounds rapidly dried up and were soon covered by skin. Even in extensive lesions a sufficiently firm covering of skin was formed without taking further measures, and provided the limbs were moved early, no contractions due to scarring were formed. A fair number of ulcers of the leg, also, after they had been cleansed by the application of moist compresses, were benefited by treatment with azodermin. Toxic symptoms were never observed after using azodermin ointment, not even when extensive areas were thoroughly treated with it.

### Barium Sulphate.

The insolubility of barium sulphate led Günther to use this salt as a means of producing shadows in Röntgen ray examinations. After C. Bachem had demonstrated in experiments on animals that the preparation passed through the intestinal tract without giving rise to any harmful results, and Günther had proved its usefulness as a means of producing contrasts, the author then tried its employment in man, giving at first small doses in order to convince himself of the absolute harmlessness of barium sulphate in the human body. As was to be expected, the preparation proved quite harmless. It is not only insoluble in water, but also in acids, and only when heated to boiling with concentrated solution of an alkaline carbonate is it partially converted into the carbonate which dissolves in acids. Thus there is no possibility, either in the stomach or in the intestine, of barium sulphate being converted into a soluble compound, which might be absorbed. Nobody has as yet proved that the organic substances present in the gastro-intestinal tract are capable of bringing about a change of this description. Besides, Günther has demonstrated the harmlessness of the salt by its employment in practice. But one condition should be observed, to which I wish to draw special attention, viz., the barium sulphate used must be

Günther-Bachem, Deutsche medizinische Wochenschrift 1911, p. 717.  
Compare also Best and Cohnheim, Münchener medizinische Wochenschrift 1911, p. 2732.

absolutely free from other soluble barium salts (such as barium chloride, barium carbonate, barium sulphide, etc.), as these are known occasionally to have a toxic effect even in comparatively small doses. For this reason I now supply a special preparation for internal use, which is carefully tested before being supplied and is issued under the designation of "Barium Sulphate extra pure for X Ray Diagnosis".

For examining the stomach and intestines Günther uses a so-called "barium meal", which is prepared by boiling 150 grammes (5 oz) of barium sulphate, 15 grammes ( $\frac{1}{2}$  oz) of mondamin, 15 grammes ( $\frac{1}{2}$  oz) of sugar, and 20 grammes ( $\frac{2}{3}$  oz) of cocoa with 500 grammes (17 oz) of water. In examinations of the œsophagus and for the localisation of the stomach, a 40 p. c. mixture of barium sulphate may be used. According to Günther, as much as 100 to 150 grammes ( $3\frac{1}{3}$ —5 oz) of barium sulphate have been administered to more than 60 persons without harm. The innocuousness of pure barium sulphate and the usefulness of Günther's method were confirmed by Bensaude and Ronneaux.

According to statements in the literature of the past year, two cases of poisoning by barium salts occurred as a consequence of mistakes, one of them being due to the use of barium sulphide. Therefore, when ordering barium sulphate, the usual abbreviation should on no account be adopted and the prescription should read: Barium sulphate for X Ray Diagnosis\*).

### Berberine Sulphate.

In my Annual Report for 1892, I alluded to the utility of berberine in weak pains, for Fellner had found that the alkaloid caused powerful uterine contractions. I advised the following prescription of the drug:

Rp. Berberin. sulph.                      0.1 gramme ( $\frac{1}{2}$  grains)

Aq. dest.                                      10.0 grammes ( $\frac{1}{3}$  oz)

Sig.: At the beginning  $\frac{1}{5}$  of a Pravaz syringeful to be injected subcutaneously every quarter of an hour and the dose to be gradually increased until the pains are sufficiently strong.

Bensaude and Ronneaux, Presse médicale 1911, p. 520.

\*) Compare Allgemeine medizinische Zentralzeitung 1911, p. 561.

— F. Nieden, Deutsche medizinische Wochenschrift 1911, No. 33.  
Fellner, Österreichische medizinische Jahrbücher 1885, p. 349.

Kurdinowski also confirmed the action of berberine of causing uterine contractions on intravenous injection into animals, and specially emphasised the value of the alkaloid in increasing the strength of the separate contractions when the pains are weak.

R. Marek has recently again investigated the action of berberine in childbirth, and was able to confirm in part the eutocic property of the preparation. In 4 cases of abortion it acted promptly. The author used it in 27 cases of weak pains. In primiparæ it was successful in 53 p.c. of the cases, but in multiparæ in only 25 p.c. As with quinine, so with berberine in successful cases, strong contraction of the uterus followed the administration of the second or third powder, which led to the spontaneous birth of the child in the course of  $1\frac{1}{2}$  to 8 hours. Berberine sulphate proved particularly successful in painful and ineffectual labour pains, which were accompanied by severe backache. In the cases which were treated, the backache disappeared after taking berberine and in the course of an hour the pains became regular, to the great relief of the patients. On the whole, the author came to the conclusion that berberine was only reliable in certain cases, as in labour pains accompanied by severe backache. But the uncertainty in the action of berberine observed by him does not tend to promote confidence in this drug, quite apart from the fact that now more reliable medicaments are obtainable. Marek gave 3 powders at intervals of 10 minutes, the first containing 0.25 gramme (4 grains), the next two 0.1 gramme ( $1\frac{1}{2}$  grains) each of berberine sulphate in capsules. In one instance he gave two doses of 0.5 gramme ( $7\frac{1}{2}$  grains) each with good results and without by-effects.

### Birch Tar.

The value of the tar preparations in the treatment of skin diseases is dealt with by G. Nobl in an interesting paper. Among the wood tars in use (*oleum rusci* or *betulæ pyroligneum*, *oleum fagi* or *pix liquida*, *oleum cadini*), birch tar (*oleum betulæ pyroligneum*), in the author's experience, possesses all the healing properties which are attributed to the other kinds of tar, but the preparation also shows their

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Kurdinowski, communicated by Marek.

Marek, Wiener medizinische Wochenschrift 1911, p. 2146.

Nobl, Zentralblatt für die gesamte Therapie 1911, p. 561.

by-effects. It is rarely necessary to employ concentrated birch tar; it is generally used in the form of ointments and pastes, the tar content of which is varied in accordance with the degree of acuteness of the affection and of the accompanying symptoms. Pityriasis rosea with slight inflammatory symptoms is quickly cured by the application of a zinc paste containing 10 p.c. of tar. Nor does lichen ruber planus, accompanied by severe itching, require a higher concentration; in this case a vehicle should be employed which acts deeply, such as lanolin. If it be desired to bring about a simultaneous irritative action, a 20 to 30 p.c. tar paste may be used and a reducing substance added. For the treatment of chronic infiltrating, scaling and itching eczema, when not too widely distributed, a mixture of vaselin and soft soap, to which 20 p.c. of birch tar and 10 p.c. of chrysarobin, or 10 p.c. of salicylic acid, have been added, can be highly recommended. The following are also useful: the addition of 0.5 to 1 p.c. of tar to ointments for seborrhœic, psoriasiform and parasitic superficial catarrhs, also tar baths for a variety of universal, severe forms of inflammation, primary exfoliative dermatitis, secondary attacks of eczema, psoriasis, lichen ruber, artificial erythrodermia and pemphigus. For this purpose a mixture is used consisting of 100 grammes ( $3\frac{1}{3}$  oz) of birch tar, 20 grammes ( $\frac{2}{3}$  oz) of solution of ammonia, 10 grammes ( $\frac{1}{3}$  oz) of gelatin (dissolved in 50 grammes ( $1\frac{2}{3}$  oz) of water) and 50 grammes ( $1\frac{2}{3}$  oz) of a 20 p.c. solution of sodium carbonate. This gelatinous mixture is hung in little gauze bags in the water of the bath, whereby it gives a perfectly clear solution. The water should be warmed to  $28^{\circ}$  or  $29^{\circ}$  C. and the patients may be left in this bath for half an hour. A tar bath may also be prepared as follows: a mixture of 75 grammes ( $2\frac{1}{2}$  oz) of birch tar to which solution of caustic potash 15 p.c. has been added and 0.25 litre of methylated spirit is allowed to flow in a thin stream into a full bath, stirring continuously.

### Bismuth Carbonate.

For the medical treatment of intestinal catarrh, R. Kolisch, based on many years' experience, recommends the following mixture:

Rp. Bismuth. carbon. 5.0 grammes (75 grains)  
Ol. ricin. 30.0 grammes (1 oz)  
Mist. gummosæ 70.0 grammes ( $2\frac{1}{3}$  oz)  
M. Sig.: One tablespoonful 3 times daily.

With regard to the administration of large doses of bismuth carbonate for Röntgen ray examinations of the stomach and intestines\*), M. Haudeck has given the most striking proof of its harmlessness, for in over 1000 cases in which this method was used he did not observe a harmful effect in a single case. But a case reported by L. Metzger shows that occasionally unpleasant by-effects do occur after the administration of large doses; a female patient was given 40 grammes ( $1\frac{1}{3}$  oz) of the preparation in porridge as a preliminary to X ray examination. After 30 hours pain and tenesmus were felt in the rectum, while the rest of the intestine was free from pain. After the rectum had been cleared out by means of enemata, whereby besides hard, black fæces a little blood was passed, the pains soon disappeared entirely, and on the following day the patient was perfectly well again. Metzger is of opinion that the bismuth carbonate caked together and acted as a foreign body, giving rise to the pains. He considers that this circumstance shows that bismuth carbonate should only be given in such large doses when there is a possibility of quickly getting rid of it by the aid of enemata.

### Bismuth Subnitrate.

H. H. Schmid made use of Beck's method of treatment of chronic suppuration with bismuth paste in a large number of cases. The bismuth paste consisted of a sterilised mixture of 33 parts of bismuth subnitrate and 67 parts of white vaseline, warmed until it became semi-fluid, and was then injected directly into the fistula, the direction of which he had carefully made out beforehand by means of a sound. Amounts up to 100 grammes ( $3\frac{1}{3}$  oz) were injected. The injection was performed slowly, under light pressure, until a certain amount of resistance could be felt and the paste either

\*) Compare Merck's Report 1908, p. 147.

Haudeck, Verhandlungen des Kongresses der deutschen Röntgen-gesellschaft in Berlin, April 1910.

Metzger, Medizinische Klinik 1911, p. 881.

Schmid, Wiener klinische Wochenschrift 1911, p. 232.

flowed out beside the syringe or escaped through another fistula. According to E. G. Beck, the injection should be continued until the patient feels pain. Too great pressure should not be used as it might tear open the wound and the paste would thus flow into the healthy tissue. According to Schmid, this method is satisfactory both to the physician and to the patient; it is practically painless, and, in his experience, affords a safe method of treatment for chronic fistulæ and abscess cavities. It is an excellent diagnostic help in discovering the size, direction and place of origin of fistulæ and abscesses, and is thus of great value as an indication for surgical procedures, preventing the performance of incomplete and therefore useless operations. The bismuth paste also possesses an excellent symptomatic action, having a favourable influence on the pain, secretion and eczema, and in some cases assists in achieving a complete cure. M. Brandes, in further testing Beck's method, came to the same favourable conclusions. With the aid of rationally carried out injections he was occasionally able to bring about the cure of extensive fistulæ in a surprisingly short time. In his opinion failures are due to a debilitated condition of the patient, copious secretion from the fistulæ, and the advance of the primary disease; for this reason advanced tuberculosis of the bones and joints show the greatest number of failures. The danger of a possible bismuth or nitrite poisoning can, according to Brandes, be avoided by substituting bismuth carbonate for bismuth subnitrate, and by reducing the amount of bismuth injected. Beck, however, considers it necessary to adopt the following precautions. If more than 100 c.c. of bismuth paste have been injected, they should not be allowed to remain in the system for longer than 3 weeks. The paste should never be left in the patient's hands for his own use and he should be examined at least twice a week. If ulcers and bluish-black discolorations form on the pharynx or the tonsils, and are accompanied by loss of weight and cyanosis, bismuth poisoning is present and should be immediately dealt with; but a bluish discoloration of the edge of the gums alone cannot be attributed to poisoning, as this sign occurs in 20 p.c. of the cases, although the patients otherwise feel well. If poisoning has

Beck, *Therapeutische Monatshefte* 1911, p. 440.

Brandes, *Deutsche Zeitschrift für Chirurgie*, Vol. 108, *Berliner klinische Wochenschrift* 1911, p. 490.

occurred, the bismuth paste must be washed out by means of injections of warm olive oil. It should not be scraped out, as the wall of the fistula would be injured, which would lead to the further absorption of bismuth.

Tytgat used a modified form of bismuth paste, consisting of 30 grammes (1 oz) of bismuth subnitrate, 60 grammes (2 oz) of vaseline, 5 grammes (75 grains) of white wax, and 5 grammes (75 grains) of hard paraffin, in several cases of tuberculous adenitis and post-osteitic fistulæ, and also obtained satisfactory results.

As a therapeutic precaution against the troubles of cæcal atony Fischler recommends, besides a special diet, light massage of the cæcal region, application of warm, moist compresses at night, avoidance of strong purgatives, and the administration of the following powder:

Rp. Bismuth. subnit.	15.0 grammes ( $\frac{1}{2}$ oz)
Magnes. lev.	15.0 grammes ( $\frac{1}{2}$ oz)
Bismuth. salicyl.	10.0 grammes ( $\frac{1}{3}$ oz)
Rad. rhei pulv.	10.0 grammes ( $\frac{1}{3}$ oz)

M. Sig.: Half to one teaspoonful to be taken in water 3 times daily after meals.

A simple method of treating varicose ulcers of the leg is, according to Duballen, as follows: The patient is made to rest in bed with the leg raised and to apply frequently fomentations of a solution of sodium bicarbonate (15:1000) until the ulcer has healed. Whereupon a dusting powder is applied for 2 to 3 days, consisting of 5 grammes (75 grains) of bismuth subnitrate, 5 grammes (75 grains) of zinc oxide and 20 grammes ( $\frac{2}{3}$  oz) of talc. The scab which forms is not to be removed. The further treatment consists in the application of zinc oxide plaster mull and of elastic bandages to the leg. This procedure is said to lead to a cure within a short time.

### Bornyval.

Bornyval, which is well known as an agreeable sedative for various neuroses and is much used in gynecological

Tytgat, Presse médicale 1911, p. 20.

Fischler, Münchener medizinische Wochenschrift 1911, p. 1235.

Duballen, Bulletin médical 1910, No. 27, Monatshefte für praktische Dermatologie 1911, Vol. 52, p. 401.

ailments, has now been introduced by Hengst into veterinary practice. It is said to render good service in the case of dogs suffering from diseases of the central nervous system. To large dogs the author gives a daily dose of 8 perles (containing 0.25 gramme [4 grains] of bornyval each), to middle-sized animals he gives 1 to 5, and to small dogs 1 to 3 perles. When given to very small dogs, the preparation occasionally displays a soporific rather than a sedative effect. In most cases of epileptic convulsions its action was excellent, as well as in cases which had previously been unsuccessfully treated with bromide preparations and sulphonal. The intervals between the attacks became longer, the attacks themselves lessened in violence and in some cases were even reduced to mere restlessness and conditions of fear. Although the author was in no case successful in curing epilepsy by the use of bornyval, he has found it a good remedy and superior to others. It should, however, not be prescribed in the presence of gastric catarrh, as it might cause vomiting and thus lead to a fresh attack. It is also useful in nervous palpitation consequent upon valvular disease, and in cutaneous irritation either with or without the formation of papules, for given in conjunction with the application of aqueous and alcoholic lotions it rapidly brings about the cure of these symptoms. But it is of little or no use in the convulsions and muscular spasms of epilepsy, or in inflammation of the brain with symptoms of mania.

A more recent communication referring to the use of bornyval in human medicine has been published by D. Isola. Like other authors, he has prescribed the drug with good results for functional disturbances of the nervous system, such as hysteria, neurasthenia and gastric neurosis. It has also been said to have proved useful in cardiac neuroses and never to have given rise to disturbing by-effects, even when given for a prolonged period in large doses, up to 10 capsules daily.

### **Bromipin.**

In a communication by S. Kalischer on functional nervous diseases of children, attention is drawn, among other

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Hengst, Berliner tierärztliche Wochenschrift 1911, p. 361.

Isola, Clinica medica italiana 1911, No. 26.

Kalischer, Zeitschrift für ärztliche Fortbildung 1911, No. 3.

points, to the medicinal treatment of migraine and epilepsy by bromine or bromipin. The latter is particularly useful in the treatment of migraine if a lengthy course of bromide treatment is necessary, for this bromine preparation has at the same time a food value. As is well known, one teaspoonful of 10 p.c. bromipin corresponds to 0.4 gramme (6 grains) of bromine, or to 0.5 to 0.75 gramme ( $7\frac{1}{2}$ —12 grains) of bromine salt. Children may therefore be given 2 to 4 teaspoonfuls of this preparation daily. It is also well borne in the form of tablets. Each bromipin tablet corresponds to about 0.4 gramme (6 grains) of bromine. In prescribing bromine preparations for epilepsy, the author considers that the doses should not be divided, but if possible one large dose should be given at night. Further, bromine should not be given continuously and in large doses if the attacks do not occur frequently. The author recommends bromipin especially for children. Diehl prescribed it in cases in which sodium bromide gave rise to bromism, and although the bromine acne did not disappear entirely, yet the by-effects were always mitigated; only in rare cases were all signs of bromine disturbance absent. If bromipin proves unpalatable on account of the taste of sesame oil, Diehl suggests that it should be given in light beer, which is said to best disguise the taste. Apart from this, beer and all alcoholic beverages, as well as coffee and tea, must be strictly avoided during the treatment of epilepsy.

For the treatment of the constipation in mucous colic H. Citron recommends the use of oil enemata, consisting of 100 grammes ( $3\frac{1}{3}$  oz) of oil to which 20 to 25 grammes ( $\frac{2}{3}$ — $\frac{5}{6}$  oz) of bromipin (10 p.c.) are added.

### **Bromural.**

According to F. Deffge, bromural has proved a useful sedative and hypnotic in psychiatry, as has also been reported by others\*). In the insomnia of hysteria and neurasthenia doses of 0.3 to 0.6 gramme (5—10 grains) bring about quiet

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Diehl, Monatsschrift für Psychiatrie und Neurologie 1911, Vol. 29.  
Citron, Beihefte zur Medizinischen Klinik 1911, No. 9.

Deffge, Dissertation Rostock 1910.

\*) Compare Merck's Report 1907—1910.

and dreamless sleep. After a week's administration of the preparation most of the patients were able to obtain several hours of sleep, even without the bromural medication, and in severe cases the author was able to reduce the dose from 0.6 to 0.3 gramme (from 10 to 5 grains). Several of the symptoms, such as fear, giddiness, palpitation, etc., were favourably influenced by the administration of bromural. E. Kraus was able to confirm this effect in the case of children, for in his experience the nocturnal restlessness and fear of the little patients subsided under treatment with bromural. The author prescribes 0.1 gramme ( $1\frac{1}{2}$  grains) for babies, and for older children 0.15 gramme ( $2\frac{1}{2}$  grains). Baravalle and C. Cattaneo have also prescribed bromural for children for various purposes. Cattaneo prescribed it, on account of its sedative properties, for pertussis and convulsions and obtained by its use marked alleviation and disappearance of the cough. It also proved useful in laryngeal spasm and eclampsia. In epilepsy, also, it is serviceable as a palliative. The author considers the preparation quite harmless, as a child 14 months old took a daily dose of 1.5 grammes (24 grains) without discomfort. Baravalle found bromural useful as a sedative for children after operations, for children usually require a sedative after and not before an operation. For this purpose 0.3 gramme (5 grains) of bromural are given after the operation, and in the evening and this medication may be continued for several days. Baravalle also achieved very good results in severe injuries, in meningitic symptoms, in chorea and tetanus, in which bromural acted successfully as a sedative. To children under 8 years of age the author gave daily doses of 0.1 to 0.6 gramme ( $1\frac{1}{2}$ —10 grains). These were, without exception, well borne.

Beeck prescribed bromural in doses of 0.6 gramme (10 grains) as a soporific for a woman aged 79, who was suffering from severe neuralgia of the brachial plexus, accompanied by complete insomnia. Besides having the desired effect, the author observed that the severe glycosuria also present was considerably reduced. But Beeck does not con-

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Kraus, Wiener medizinische Zeitung 1910, No. 42.

Baravalle, La Pediatria 1910, No. 12.

Cattaneo, Rassegna di pediatria 1910, No. 10.

Beeck, Allgemeine medizinische Zentralzeitung 1911, No. 25.

sider bromural a specific for diabetes, and thinks that the improvement was due to the sleep occasioned by the drug.

The harmlessness of bromural is evident from two occurrences reported by E. Rieger and A. Müller. In both cases the patient had, against the doctor's orders, taken very large doses of bromural (3, 6 or 9 grammes) [45, 90 or 135 grains], without suffering permanent harm.

A communication of Göschel's may be referred to, in which the author discusses his experience of bromural in stage practice. He points out that bromural may be used successfully, without interfering with the patient's professional duties, as a hypnotic and sedative for nervous individuals or those having a neuropathic tendency, who daily have to do arduous mental work.

### Cacodylates.

The attempts made to treat syphilis, apart from the use of mercury and iodine, with the most harmless and effective preparations of arsenic is the reason why the cacodylates\*), and especially sodium cacodylate, have again passed into the foreground of therapeutic interest, as is apparent from numerous publications during the past year. Communications have been published by W. J. Barlow and R. L. Cunningham, A. J. Caffrey, Z. W. Crigler, Spencer L. Dawes, M. Lion, di Mattei, E. Müller, H. J. Nichols, Rille,

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Rieger, Münchener medizinische Wochenschrift 1911, No. 5.

Müller, Deutsche medizinische Wochenschrift 1911, No. 8.

Göschel, Klinisch-therapeutische Wochenschrift 1911, p. 1160.

\*) Compare Merck's Report 1910, p. 1.

Barlow, Cunningham, Journal of the American Medical Association 1911, Vol. 57, p. 1435.

Caffrey, Journal of the American Medical Association 1911, Vol. 56, p. 641.

Crigler, Journal of the American Medical Association 1911, Vol. 56, p. 897.

Dawes, Journal of the American Medical Association 1911, Vol. 57, p. 480.

Lion, Berliner klinische Wochenschrift 1911, p. 1420.

Mattei, Gazzetta degli ospedali e delle cliniche 1911, No. 58.

Müller, Münchener medizinische Wochenschrift 1911, p. 713.

Nichols, Journal of the American Medical Association 1911, Vol. 56, No. 7.

Rille, Therapeutische Monatsberichte 1911, p. 186.

A. Robin, H. A. Schirrmann, O. L. Suggett, P. N. Prokhorow, and others.

Sodium cacodylate has almost invariably proved highly satisfactory in syphilis. Schirrmann, in several cases of obstinate tertiary syphilis and of primary chancre, obtained almost wonderful results by using subcutaneous doses of 0.2 gramme (3 grains). With no other medication has he ever had such excellent results as with this treatment with cacodylic acid. Suggett obtained equally favourable results in secondary and tertiary lues, and also in hemiplegia, whereas the preparation proved less effective in primary syphilis. The author strongly recommends the use of sodium cacodylate, especially for congenital syphilis. As a dose he suggests up to 0.6 gramme (10 grains) a day. In hemiplegia he has given 27 injections, each consisting of 0.18 gramme (3 grains) of sodium cacodylate at intervals of 1 to 7 days. Caffrey, who used sodium cacodylate with excellent results for primary sclerosis of the upper lip, considers the drug to be just as good as salvarsan. The great value of sodium cacodylate has been confirmed by Crigler in rupia syphilitica, by Dawes in skin diseases, and by Prokhorow in various syphilitic affections. But whereas Dawes successfully prescribed doses of 0.1 to 0.3 gramme ( $1\frac{1}{2}$ —5 grains) in anæmia, Prokhorow considers large doses to be necessary in syphilis, and gives 0.1 gramme ( $1\frac{1}{2}$  grains) for each kilogramme of body-weight, so that, for example, a man weighing 70 kilogrammes would receive an injection of 7 grammes of sodium cacodylate. Such large doses are somewhat startling, but before giving an opinion on the subject, it will be well to wait and see whether the experiments of other investigators confirm Prokhorow's statements. According to the author's instructions, the skin at the site of the injection is disinfected with tincture of iodine and then the injection fluid is freshly prepared by dissolving 7 grammes (105 grains) of sodium cacodylate in 3 to 4 c.c. (50—68 min.) of water and the solution is sterilised by boiling in a test-tube over an open flame. Although the solution is very con-

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Robin, *Médecine moderne* 1910, 24<sup>th</sup> December. — *Revue de thérapeutique* 1911, p. 131.

Schirrmann, *New York Medical Journal* 1911, 8<sup>th</sup> April, p. 676.

Suggett, *New York Medical Journal* 1911, 8<sup>th</sup> April, p. 674.

Prokhorow, *Presse médicale d'Égypte* 1911, p. 188.

centrated, it is said to cause no local symptoms of irritation and to be very quickly absorbed, for in the course of a few minutes the patient's breath is said to assume the well known characteristic odour, which disappears in 3 to 4 days. In this time the elimination of the cacodylate will probably have taken place. The injection may be repeated every 5 days, unless it is preferred to begin with smaller doses (0.02 gramme pro kilogramme of body-weight), when the interval may be reduced. These large doses are said to cause neither considerable pain nor by-effects such as rise in temperature or disturbance of vision. The author has only in exceptional cases observed giddiness or headache, and very rarely erythema. The success of this method became apparent in a short time by the retrogression of the syphilitic efflorescences and by the improvement in the general health. Prokhorow therefore considers sodium cacodylate to be an excellent antisyphilitic when given in large doses, and to have the advantage over mercury of causing slighter by-effects.

In the secondary anæmia of tuberculosis Barlow and Cunningham used sodium or ferric cacodylate with satisfactory results. Injections of ferric cacodylate are, in their experience, indicated if the percentage of hæmoglobin in the patients' blood is comparatively low. 0.03 gramme ( $1\frac{1}{2}$  grain) is given 2 to 3 times a week, a different site being chosen for each injection. But if the patient is neurotic or is afraid of the pain of the injections, then sodium cacodylate is used. The latter is also to be preferred if syphilis is suspected. In these cases 1 c. c. (17 min.) of a 13 p. c. solution of sodium cacodylate is injected at first 3 times a week and later twice, viz., 0.13 gramme (2 grains) of sodium cacodylate for a dose. If a substitute is required for ferric cacodylate in secondary anæmia, in order to avoid the use of a painful injection fluid, 1 c. c. (17 min.) of a 5 p. c. solution of sodium cacodylate may be used to begin with. If the hæmoglobin content of the blood is not too low, sodium cacodylate is preferable in any case\*).

For the treatment of hemiplegia due to syphilis Robin suggests the subcutaneous injection of the following solution:

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\*) Compare also the article on "Strychnine Cacodylate" in this Report.

Rp. Sod. cacodyl.	0.1 gramme	(1 $\frac{1}{2}$ grains)
Hydrarg. iod. rubr.	0.1 gramme	(1 $\frac{1}{2}$ grains)
Pot. iodid.	0.1 gramme	(1 $\frac{1}{2}$ grains)
Aq.	10.0 grammes	(1 $\frac{1}{3}$ oz)

For daily use 1 c. c. (17 min.) of this solution is injected at first, increasing the dose by 1 c. c. (17 min.) daily, until a dose of 5 c. c. (85 min.) is reached. The author supplements this treatment by massage, exercises, baths and other physical measures.

A combination of sodium cacodylate with extractum cerebri, the so-called "arsenocerebrin" has been used by. Lion in 150 cases of epilepsy, and he claims to have obtained good results. According to the severity of the case, he injected 2 c. c. (34 min.) of arsenocerebrin 3 to 6 times a week. If there was a decrease in the number of attacks, which was generally the case in the course of 2 to 3 weeks, he diminished the dose. The total disappearance of the fits is said to occur in 2 to 3 months, and recurrences are said to be avoided by continuing the treatment for another 3 months. In severe cases the treatment should be continued for 10 months. Besides arsenocerebrin the author prescribed 1 to 2 grammes (15—30 grains) of a bromide salt daily, and a suitable diet.

### Calcio-Phosphate of Uranium.

As a substitute for radium, A. Churchward suggests the use of calcio-phosphate of uranium, which occurs as a mineral, and, according to his investigations, is radio-active. As a precaution he considers it desirable to test the mineral before use by allowing it to act for 3 to 6 hours on a photographic plate. The author treated 3 cases of rodent ulcer with excellent results by irradiation with the mineral. One case was completely cured in 5 weeks, another in 9 weeks, and in the third case the ulcer was reduced to a tenth of its original size. The calcio-phosphate of uranium was applied on lint and held in position by bandages. If the reaction is not too intense the duration of the application may be fixed at 3 to 5 hours a day. Should dermatitis occur, the treatment should be reduced to an hour. To prevent loss the mineral should be wrapped in gauze which is then applied to the affected part.

**Calcium Chloride and Calcium Lactate.**

The communications of R. Chiari and H. Januschke on the action of calcium chloride in preventing transudation and exudation are of considerable theoretical and practical interest. These two workers succeeded, by sufficiently enriching the system with calcium salts, in preventing or much reducing the formation, on the one hand, of pleural effusions in dogs and guinea-pigs produced by poisoning with sodium iodide, thiosinamin and diphtheritic toxin, and on the other hand, the inflammatory œdema of the conjunctiva of the rabbit's eye after the instillation of mustard oil and abrin. Calcium chloride has the most powerful preventive action, and next to it calcium lactate. The action of calcium salts in preventing the formation of exudates occurs three hours after intravenous injection, and disappears 24 hours after subcutaneous injection. According to the authors, this action is entirely independent of the property possessed by calcium salts of facilitating the clotting of blood. It is evident that these results offer good prospects for the use of calcium chloride in practice. I have in my Reports several times discussed the considerable healing properties displayed by calcium medication in certain skin affections, such as urticaria, serum exanthemata, etc. The experiments of the above cited authors encourage the employment of calcium medication for transudations and exudations of other organs. Thus, in hay fever and other forms of rhinitis accompanied by copious secretion, the administration of 3 to 4 grammes (45—60 grains) of calcium lactate a day removed, or reduced, the secretion within two days. Again, in individuals sensitive to iodine, similar doses of calcium lactate prevented the appearance of the typical symptoms of iodism (iodine coryza, conjunctivitis, and laryngeal catarrh).

R. Levy considers that the action of calcium chloride in preventing transudation and exudation described by Chiari and Januschke has not been proved, and thinks that the injections of the salt may give rise to difficulties; he remarks: "Since a 5 p.c. solution cannot be employed subcutaneously on account of its strongly irritative action, lower concentrations

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Chiari-Januschke, *Wiener klinische Wochenschrift* 1910, p. 427 and

*Archiv für experimentelle Pathologie* 1911, Vol. 65, p. 120.

Levy, *Berliner klinische Wochenschrift* 1911, p. 1322.

must be used which necessitates the administration of larger quantities of fluid. But it does not appear reasonable, according to the clinical views held at present, to attempt to exert a favourable influence on transudations and exudations by means of copious infusions, especially as Loeb, Fleisher and Hoyt have shown that the administration of calcium chloride considerably reduces the renal secretion and favours the appearance of pulmonary oedema." H. Meyer, on the other hand, asserts that calcium salts have the power of diminishing the permeability of the vessels, thus to a certain extent confirming Chiari's results.

H. Leo's results were similar to those of Chiari. In his experience, however, calcium salts act more promptly when injected subcutaneously than when applied intravenously. When 2.5 to 5 p.c. solutions were used, they caused symptoms of local irritation, but these may be avoided if only 1 c.c. (17 min.) of the 2.5 p.c. solution is injected at a time, and the injection repeated in various parts of the body. Internal administration is also effective, though it may take a day before the action is evident; rectal administration, however, is without effect. As the author observed a healing action to follow its local application to the mucous membrane in conjunctivitis produced experimentally by mustard oil, he feels justified in recommending the experimental use of calcium chloride solution for inflammatory conditions of the mucous membranes of the mouth and throat.

On account of the importance of calcium salts to the pathology and physiology of metabolism, the investigations of N. Voorhoeven also deserve consideration. By testing human blood after the administration of large doses of calcium by mouth, he came to the conclusion that by the daily administration of 2727 milligrammes of CaO, in the form of calcium chloride or calcium lactate, the calcium content of the blood can be considerably increased in adults by giving a diet rich in calcium. By giving an additional amount of 545 milligrammes of CaO a day, the increase of calcium in the

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Loeb, Fleisher, Hoyt, *Zentralblatt für Physiologie* 1908, Vol. 22, p. 496.

Meyer, *Zeitschrift für Balneologie, Klimatologie etc.*, Vol. III, No. 15. — *Semaine médicale* 1911, p. 455.

Leo, *Deutsche medizinische Wochenschrift* 1911, p. 5.

Voorhoeven, *Biochemische Zeitschrift* 1911, Vol. 32, p. 394.

blood, under identical conditions, is in most cases either less than 2.5 milligrammes in 100 c.c., or no increase is demonstrable. The increase in the proportion of calcium in the blood may last for weeks. No untoward effect was observed on giving large doses of calcium.

While the diuretic action of calcium chloride in nephritis and albuminuria has been pointed out by various observers, Bonnamour, Imbert and Jourdan have, on prescribing the salt, also observed an increase in the elimination of sodium chloride and have determined it quantitatively in 15 cases. In 9 cases the diuretic effect resulting from daily doses of 0.3 to 2.0 grammes (5—30 grains) was unmistakable, in 6 cases it was absent. In the experience of the authors, calcium chloride medication, especially for symptoms of nephritis appearing in the course of infective diseases, should be preferred to a salt-free diet. This is also confirmed by Vitry.

E. Meyer has also reported upon the use of calcium chloride in the tetany of pregnant women. In one case, among others, after several vain attempts at treatment with other measures, he prescribed three tablespoonfuls of an aqueous solution of calcium chloride (8:200), in addition to a diet poor in salt but rich in calcium, and by this means he completely changed the course of the disease within a few days. The pains disappeared, and the contractions ceased. If the tetanic symptoms reappeared and proved more obstinate than the first time, the author prescribed larger doses with equally good results, giving 4 grammes (60 grains) of calcium chloride (in 100 grammes [ $3\frac{1}{3}$  oz] of water) daily.

### Camphor.

The treatment of inflammation of the lungs by means of injections of camphor, which has been recommended by various authors, was tried by L. Weber in a case of pneumonia accompanied by severe pneumococcic infection, with a remarkably good result. In consequence of the injections the disease ran a favourable course, and neither local irritation at the site of injection nor by-effects in the bladder, the kidneys or the stomach were observed. The treatment consisted in hourly

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Bonnamour, Imbert, Jourdan, *Lyon médical* 1911, No. 4, p. 148.  
Vitry, *Presse médicale* 1911, p. 633. — *Revue de thérapeutique* 1911, p. 571.

Weber, *Medical Record* 1911, 28<sup>th</sup> January.

injections of 1 c. c. (17 min.) of a 20 p. c. solution of camphor in olive oil, 8 injections being given daily. Volland also strongly advises the use of injections of a 10 p. c. solution of camphor in oil for the treatment of cardiac debility in pneumonia.

The internal antiseptic action of camphor observed in pneumonia is, according to F. Weitlaner, also very effective in tuberculosis. The subcutaneous injection of camphor combined with the internal administration of salicylic acid is said to have been of considerable value in pulmonary tuberculosis. Weitlaner prescribes the following mixtures for this purpose:

Rp. Camphor.	15.0 grammes	15.0 grammes
Iodoform.	10.0        "	10.0        "
Cetacei	20.0        "	50.0        "
Ol. Sesam.	80.0        "	50.0        "

On heating on a water-bath, the mixture dissolves to form a clear yellow mass, which must be liquefied by warming each time before use. Every 4 to 8 days, 6 to 10 c. c. of this mixture are injected under the skin of the abdomen, previously anæsthetised by the injection of a few drops of a 5 p. c. cocaine solution. The injection of the warmed solution of camphor, iodoform and fat is administered by means of a suitable syringe held parallel to the skin and injected deep into the subcutaneous tissue, to the left and right of the linea alba. The puncture wound is then covered over with salicylic plaster. The deposit of camphor and iodoform thus formed is absorbed within a few days, and by this method of treatment the patient is able to follow his occupation without interference. The patient should take 3 to 4 grammes (45—60 grains) of the following powder daily, in order to avoid complications:

Rp. Sod. salicyl.	30.0 grammes (1 oz)
Pulv. ipecac. co.	3.6 grammes (55 grains)

Divide in p. æq. No. XX. Sig.: 1 powder to be taken 3 to 5 times daily.

At the commencement of the treatment, and in the most severe cases, the author states that by his method the results have been amazing. But he is unable to say when the desired result will be attained, and even confesses that the treatment

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Volland, *Therapeutische Monatshefte* 1911, p. 596.

Weitlaner, *Klinisch-therapeutische Wochenschrift* 1911, p. 574.

must occasionally be continued for months or even for a lifetime. It is not only useful in pulmonary tuberculosis, but also in miliary tuberculosis and tuberculous cerebro-spinal meningitis. For superficial tubercular affections of the skin, Weitlaner recommends the following two prescriptions as being specially valuable:

Rp. Camphor. 4.0 grammes (60 grains)

Plumb. acet. 4.0 „ (60 „ )

Ung. simpl. ad 100.0 „ ( $3\frac{1}{3}$  oz)

M. Ft. ung.

Rp. Camphor. 5.0 grammes (75 grains)

Emplast. sapon salicyl.

(10 p. c.) ad 100.0 „ ( $3\frac{1}{3}$  oz)

M. Ft. emplast.

In the treatment of phthisis a solution of camphor in oil, according to Volland, constitutes a most valuable drug, particularly because even in large doses it never does any harm. He has himself injected subcutaneously as much as 30 grammes (1 oz) of a 10 p. c. solution of camphor in oil within 24 hours in severe pulmonary hæmorrhage, without detecting any unpleasant consequences. The injections proved of great use.

In the treatment of peritonitis, also, the use of a solution of camphor in oil continues to gain in favour. G. Hirschel and A. Krecke have communicated their experiences on this subject. Hirschel, after removing the suppurating centre and wiping away the pus, treated the diseased peritoneum with a warmed 1 p. c. solution of camphor in oil, of which he used up to 300 grammes (10 oz). The camphor administered in this way exerts a lasting, favourable influence on the heart, and on intestinal peristalsis, while the oil prevents the formation of adhesions and intestinal kinks. Krecke had equally good results; in 11 cases of operations on the appendix he treated the suppurative peritonitis with a solution of camphor in oil. He poured 100 grammes ( $3\frac{1}{3}$  oz) of a 1 p. c. solution of camphor in oil into the peritoneal cavity and distributed it in all directions by means of a swab, whereupon he closed and drained the wound. By this method of treat-

Hirschel, Zentralblatt für Chirurgie 1911, No. 30.

Krecke, Monatsschrift für Geburtshilfe und Gynäkologie 1911, Vol. 33.

ment he had not a single fatal case, whereas in former years the mortality in the author's clinic amounted to 34 to 42 p.c. O. Burckhardt, Kolb and O. Hoehne have also expressed a favourable opinion as to the value of a solution of camphor in oil in already established peritonitis, and especially as a prophylactic against post-operative peritonitis.

A communication of von Budberg's draws attention to the analgesic and antiseptic action of camphor in gynecological practice; he has used camphor successfully for years in perimetritis, parametritis, salpingitis and other inflammatory conditions of the pelvis. He plugged the vagina with cotton wool soaked in a 2 p.c. solution of camphor in glycerin to which he added a 10 p.c. boric acid solution, and in the presence of gonorrhœa a 2 p.c. alumol solution. The plugs were changed 3 times daily. This treatment always alleviated the pains, and even seemed to bring the pelvic abscesses to a head more quickly.

### **Carbolic Acid.**

A communication of G. Baccelli's on the treatment of tetanus, and especially of severe cases, is of considerable interest. According to his carefully collected statistics of the published cases of tetanus treated by injections of phenol, the mortality of tetanus has decreased considerably under phenol treatment. In severe cases the mortality has fallen from 100 p.c. to 2.12 p.c., and in very severe cases from 100 p.c. to 18.5 p.c. If, therefore, severe tetanus which is incurable spontaneously, has through phenol injections been cured in 98 p.c. of the cases, and a cure has been obtained in 81 to 85 p.c. of the cases of very severe tetanus, in which death as a rule takes place with dramatic violence in 24 to 48 hours, Baccelli's suggestion to give phenol injections in these cases must be applauded. In the author's experience sufficiently large doses of phenol injected subcutaneously or intravenously constitute the fundamental requirement

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Burckhardt, Zentralblatt für Gynäkologie 1911, No. 33.

Kolb, Korrespondenzblatt für Schweizer Ärzte 1910, No. 35.

Hoehne, Zentralblatt für Chirurgie 1911, No. 33.

von Budberg, Zentralblatt für Gynäkologie 1911, No. 37.

Baccelli, Berliner Klinische Wochenschrift 1911, p. 1021.

which leads to favourable results. These are well borne because, according to Baccelli, tolerance for a powerful acting remedy, such as phenol, stands in direct proportion to its indication. The single dose, the author states, often exceeded 0.1 to 0.15 gramme ( $1\frac{1}{2}$ — $2\frac{1}{3}$  grains) and the dose could be increased without ill-effects to 0.75 gramme (12 grains) in a boy 9 years old, to whom this dose was given every 12 hours for 12 days. Another patient bore 3 grammes (45 grains) of phenol daily for 14 days without harm. As regards the kind of phenol solution used, Baccelli employed a 2 to 3 p.c. aqueous solution in daily doses not exceeding 0.3 to 0.5 gramme ( $5$ — $7\frac{1}{2}$  grains) to begin with. As soon as the tolerance of the patient had been ascertained, the urine being carefully watched meanwhile, he raised the daily dose without special precautions to 1 or 1.5 grammes ( $15$ — $24$  grains), divided into several injections given in the course of 24 hours. Larger amounts can only be recommended in very severe cases and must be given with great care and increasing gradually. In order to modify the local reaction, especially in children, the 5 p.c. oily solution suggested by Maragliano may be used.

Baccelli's method might also prove successful in veterinary medicine. Thus J. Hajnal treated a pregnant mare suffering from tetanus with daily subcutaneous injections of 20 grammes ( $\frac{2}{3}$  oz) of a 2 p.c. solution of phenol, with the result that the spasms ceased and 15 days after the commencement of the illness a perfectly healthy foal was born. Five weeks later the mare was fit for work. The author was also successful in curing a sucking foal in 4 weeks with daily subcutaneous injections of 10 grammes (150 grains) of the 2 p.c. solution. Besides subcutaneous injections, horses may be given a 0.5 p.c. phenol solution rectally.

H. Vallow claims that he has obtained good results in pulmonary tuberculosis with intrascapular injections of a 1 p.c. sterile phenol solution. He injected 0.1 to 0.2 c. c. of this solution at intervals of 8 days, with the result that in most cases the general health and expectoration were improved.

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Maragliano, reported by Baccelli l. c.

Hajnal, Allatorvosi Lapok 1910, No. 15. — Berliner tierärztliche Wochenschrift 1911, p. 292.

Vallow, British Medical Journal 1911, II, p. 106.

### Carbonic Acid.

The treatment of diseases of the skin with carbonic acid snow\*) has been discussed by A. Strauss, H. Fründ, G. Nobl and H. Springels, Grintschar, Lichtmann, A. Salomon, J. L. Bunch, J. Douglas, Hinrichs, M. Kuznitsky, J. Fabry, W. Stelwagon and Favera.

The technique of the treatment with carbonic acid snow is described in detail by Strauss, who points out that the effect is dependent upon various factors, such as the length of time of its action, the pressure, the sensitiveness and the resisting power of the skin. Fründ also discusses the technical aspect of the employment of carbonic acid, and draws attention to the good results obtained in cases of indolent varicose ulcer by touching the callous edges with carbonic acid snow. This treatment is said to be very simple and should be more widely used. Other indications for the use of carbonic acid, according to the authors named, are nævi vasculosi and pigmentosi, warts, epitheliomata of the skin, tuberculosis verrucosa, lupus vulgaris and erythematodes, keloids, clavi, angiomatica, angiocavernomata, etc. I described the method in sufficient detail last year.

Montagu Harston also used the carbonic acid pencil in 15 cases of trachoma and states that in most of the cases a cure resulted. He turned back the eye-lids and allowed the carbonic acid to act for 15 seconds, and later for 20 to 30 seconds, upon the conjunctival fold and then

\*) Compare Merck's Report 1910.

Strauss, Münchener medizinische Wochenschrift 1911, p. 27.

Fründ, Münchener medizinische Wochenschrift 1911, p. 29.

Nobl-Springels, Zeitschrift für physikalische und diätetische Therapie Vol. 14, No. 7 and 8.

Grintschar, Monatshefte für praktische Dermatologie 1911, Vol. 52, p. 72.

Lichtmann, Russkij Wratsch 1910, No. 30.

Salomon, Deutsche Zeitschrift für Chirurgie 1911, Vol. 109, No. 5.

Bunch, British Medical Journal 1911, I, p. 247.

Douglas, New York Medical Journal 1910, 24th December.

Hinrichs, Deutsche medizinische Wochenschrift 1911, p. 1676.

Kuznitsky, Münchener medizinische Wochenschrift 1911, p. 513.

Fabry, Dermatologische Zeitschrift 1911, No. 8.

Stelwagon, Therapeutic Gazette 1910, August.

Favera, Giornale italiano delle malattie veneree e della pelle 1911, No. 2.

Harston, British Medical Journal 1911, II, p. 107.

upon the conjunctiva tarsi. The pain caused by this application is said to be similar to that which occurs after cauterising with lunar caustic.

### Chinosol.

J. McElroy used chinosol in combination with formaldehyde for intravenous injections in pulmonary tuberculosis and states that the results were excellent. In the author's opinion, the two drugs have a destructive action on the tubercle bacilli; he has observed that they entirely disappear under this treatment, and Sinton noticed that they became more granular in type. For injection McElroy used a solution which contained 1 part of formaldehyde in 2000 parts and 1 part of chinosol in 4000 parts. In one case he injected 50 c.c. of this solution daily on 33 consecutive days. Gradually the concentration of the fluid to be injected may be increased, until the mixture contains 1 part of formaldehyde in 500 parts and 1 part of chinosol in 1000 parts. According to the author's report, the subjective and objective symptoms practically disappear under this treatment. Very soon no tubercle bacilli can be demonstrated in the sputum; in one case the author noticed that none reappeared. Apart from slight stomach trouble, the treatment is said to give rise to no unpleasant by-effects.

This favourable report induced K. Blühdorn to test the method pharmacologically, and his results clearly showed that the two antiseptics, chinosol and formaldehyde, exercised no influence whatever either on the commencement or on the course of a tuberculous infection. The author, therefore, no longer employs this method for his patients.

### Chloral Hydrate.

Rehse gives his experiences as to the utility of chloral hydrate as a narcotic in veterinary surgery. According to him,

McElroy, *Lancet* 1910, p. 1408 (12<sup>th</sup> November). The statement as to the concentration of the chinosol-formaldehyde solution used is expressed in the original paper in such a way that it is uncertain whether the author refers to a solution containing 0.50/100 formaldehyde and 0.250/100 chinosol, or whether equal parts of these solutions, viz., 25 c.c. of each, are to be used for an injection.

Blühdorn, *Deutsche medizinische Wochenschrift* 1911, p. 1882.

Rehse, *Monatshefte für praktische Tierheilkunde*, Vol. 21, p. 413.

— *Berliner tierärztliche Wochenschrift* 1911, p. 77.

the subcutaneous, intratracheal or intravenous application of the drug is of no use for horses, nor is the rectal employment much more satisfactory. The best method of application is by mouth, and this gives rise to no difficulty if the chloral hydrate solution is well diluted. Too large doses cannot be recommended for operative procedures, as the anæsthesia would last longer than necessary. It is better, should the anæsthesia prove insufficient, to use a local anæsthetic or to give chloroform inhalation. Chloral hydrate anæsthesia has the following advantages: it need not be supervised by a specialist, no untoward by-effects and no complications are, as a rule, to be feared, the animal's strength is overcome before it lies down, so that it does not offer resistance and the danger of fractured bones is thus diminished. Even vicious horses are said to lie down readily after having taken chloral hydrate internally. The action usually commences in 10 minutes and is just as effective as when the drug is administered intravenously. If the chloral hydrate solution is not taken, its rectal administration may be adopted, for which a larger dose is necessary. According to Rehse,  $2\frac{1}{2}$  times as much chloral hydrate is required when given rectally. With regard to the dosage, my previous Report should be consulted\*).

### Chloretone.

Chloretone has frequently proved of use as an antispasmodic, indeed McClintock and Hutchings affirm that it even surpasses all other remedies used for spasm on account of its reliability. R. A. Hobbs confirmed this statement, for he obtained an excellent result in a case of tetanus by the use of chloretone. After the injection of a dose of tetanus serum he administered 2.4 grammes (36 grains) of chloretone in olive oil per rectum, 2 or 3 times in the course of 24 hours, for several consecutive days; this drug is said to be safer and simpler than the lumbar application of magnesium sulphate. In the case described by the author, the treatment led to an improvement in the symptoms and to a cure in a short time. The prompt action to which the author refers

\*) Merck's Report 1910, p. 141.

McClintock—Hutchings, comp. E. W. Sheaf, British Medical Journal 1910, p. 1402 (5<sup>th</sup> November).

Hobbs, British Medical Journal 1910, p. 1402 (5<sup>th</sup> November).

may be chiefly due to the relatively high dosage. In order to test this method further, St. J. Croley treated an acute case of tetanus by administering chloretone per rectum in 5 doses of 1.2 grammes (20 grains), and 9 doses of 1.8 grammes (28 grains), and was well satisfied with the result.

A. Welsh reports on the value of chloretone in seasickness, having tested it on a fairly long sea voyage both on himself and on other passengers. He gave doses of 0.3 to 0.6 gramme (5 to 10 grains) as soon as vomiting commenced or a feeling of sickness was experienced, and was always successful, thereby confirming former experiences.

H. Jenny has been successful in his use of the so-called chloretone-inhalation in affections of the respiratory organs. This is a solution of 1 gramme (15 grains) of chloretone, 2.5 grammes (38 grains) of menthol, 2.5 grammes (38 grains) of camphor and 0.5 gramme (8 min.) of cinnamon oil in 93.5 grammes (3 $\frac{1}{2}$  oz) of liquid paraffin. It is applied on cotton wool, or in the form of sprays. Jenny has also applied it by means of a laryngeal spray in catarrh of the larynx or trachea, and in bronchial catarrh. In laryngeal catarrh a dose of 0.5 c. c. (8 min.) is used, and in tracheal and bronchial catarrh 1 c. c. (17 min.). The part is sprayed during a deep inspiration. The preparation is said to be always well borne and to give immediate relief without harassing the patient.

### Chlorine, Solution of.

P. Knapp states that the treatment of keratitis dendritica, an affection of the cornea which often considerably affects vision, is not treated with sufficient attention on account of the rarity of its occurrence. By means of cauterisation, as recommended by Ammann, the author has obtained satisfactory results, even in old cases with indolent ulcers; but by this method there is always the risk of scraping healthy tissue with the fine platinum loop and thus increasing the cicatricial opacity. There is special justification for this fear when the disease is situated centrally. Hence for two years

Croley, Indian Medical Gazette 1911, p. 336.

Welsh, Lancet 1911, p. 1699 (24<sup>th</sup> June).

Jenny, Therapie der Gegenwart 1911, p. 384.

Knapp, Klinische Monatsblätter für Augenheilkunde 1911, Vol. 49, p. 81.

Ammann, Archiv für Augenheilkunde Vol. 61.

he has used a method which is free from this disadvantage. It consists in scraping the diseased part and then painting it with solution of chlorine, a method suggested by other authors\*) for the treatment of recurring corneal erosions. Of 4 fresh cases treated in this way one healed in 2 days, one in 3 days, one in 5 and one in 6 days, without leaving a scar. An older case with a deeper ulcer was healed in 10 days. The unexpectedly rapid cure observed by the author in these 5 cases prompts him to recommend his method for further trial.

### Chloroform.

As it has long been known that during chloroform and ether anæsthesia the temperature of the body is lowered, and as the great fall of temperature of the gas mixture to be inhaled in the drop method of anæsthesia may be partially responsible for the development of pneumonia, A. L ä w e n has studied the question as to whether post-operative pneumonia can be avoided by warming the anæsthetic before it is inhaled. He therefore experimented with an apparatus by means of which the chloroform and ether vapours could be warmed. But the author's results showed that pneumonia cannot be thus avoided, though he does not doubt that a small proportion of cases of post-operative pneumonia may be prevented by the proposed modification of the method of inhalation anæsthesia. He considers that the warmed anæsthetics are only suitable for prolonged abdominal operations and for operations in which the wounds are extensive, such as in amputation of the breast. He also considers the warmed anæsthetic to be indicated for patients who have lost much blood or who are suffering from shock.

It is known that years ago the use of chloroform was suggested as an antidote for cases of poisoning by nitrous gases. As the scientific explanation of this suggestion was not known, F. C u r s c h m a n n, in order to clear up the question, performed experiments with nitrous gases on animals, which showed that according to the concentration of

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\*) Compare Franke, *Klinische Monatsblätter für Augenheilkunde* 1906, I, p. 508, and Kaufmann, *Klinische Monatsblätter* 1907, I, p. 202.

L ä w e n, *Münchener medizinische Wochenschrift* 1911, p. 2097.

C u r s c h m a n n, *Deutsche medizinische Wochenschrift* 1911, p. 1025.

the nitrous gases inhaled, the animals perished either in 1 to 2 hours, or after one day. The gases have a corrosive action. As a result of his investigations, the author came to the conclusion that chloroform could be of no use as an antidote to nitrous gases, and might even be harmful. In its place inhalations of oxygen or venesection are recommended.

Chloroform was recommended for internal use in typhoid by van de Moer in a 0.5 p.c. aqueous solution, to be taken in tablespoonfuls. As Conradi had also shown that chloroform has a favourable influence on the elimination of typhoid bacilli from the gall-bladder, M. Bully, in experiments on rabbits and man, attempted to prove the truth of this statement. In experiments on animals he was successful, but in man the method failed completely, even if chloroform was administered daily for a prolonged period.

### Chloro-Meta-Cresol.

As I reported last year\*), chloro-meta-cresol is an excellent antiseptic and appears to be specially suitable for the disinfection of the hands. This is confirmed in the communications of R. A. Jeney and S. Gottschalk. According to Jeney, the best preparation for this purpose is a solution of 1 part of chloro-meta-cresol in 100 parts of acetone-alcohol (a mixture of acetone and alcohol 1+2). The hands are first washed for half a minute in warm soap and water without using a nail brush; the nails are then cleaned and the hands treated for 4 minutes with the solution of chloro-meta-cresol mentioned above, using a soft brush or a piece of flannel. After this procedure the skin surface is said to be sterile. In his gynaecological practice Gottschalk used "Eusapyl", an aqueous solution of chloro-meta-cresol in potassium ricinoleate. This preparation was tested by Laubenheimer and Okada,

van de Moer, Tijdschrift voor Geneeskunde 1911, No. 12. Conradi, communicated by Bully.

Bully, Zeitschrift für Hygiene und Infektionskrankheiten 1911, Vol. 69, No. 1.

\*) Merck's Report 1910, p. 141.

Jeney, Wiener medizinische Wochenschrift 1911, p. 1363.

Gottschalk, Deutsche medizinische Wochenschrift 1911, p. 928.

Laubenheimer, Phenol und seine Derivate als Desinfektionsmittel  
Published by Urban and Schwarzenberg 1909.

Okada, Untersuchungen über Händedesinfektion. Published by  
C. G. Röder, Leipzig 1910.

who confirmed its powerful disinfecting action. Gottschalk dissolved 10 grammes of eusapyl in 900 grammes of alcohol (80 p. c.) and 90 grammes of boiled water and used this solution, which has a faint smell of chlorine and which gives rise to a transitory burning sensation on the skin, for the disinfection of the hands in the following way: The hands are washed for 5 minutes in running hot water with soft soap and a brush, then the nails are cleaned and cut. Now the hands and arms are thoroughly rubbed with soap spirit, using a piece of sterile gauze, and then thoroughly disinfected for about 5 minutes in the eusapyl solution, using a brush or a piece of flannel. This method was used for a year in the author's clinic for all aseptic procedures of a gynaecological or obstetrical nature (without the use of rubber gloves), without the occurrence of an infective rise of temperature or of a case of death. The hands were protected by rubber gloves for the performance of septic operations. Gottschalk considers the method described to be reliable, so long as the hands are not brought into contact with septic matter.

Besides this, Gottschalk used a 1 p. c. solution of eusapyl in water (corresponding to 0.5 p. c. of chloro-meta-cresol) for vaginal and intra-uterine douches. If no distilled water can be obtained for the preparation of the aqueous solution, with which eusapyl forms a clear solution, water is used which has been previously boiled, to a litre of which 10 grammes of eusapyl are gradually added, stirring continuously. This douche is well borne by the vagina and the uterus.

### Chloromorphide.

$\alpha$ -chloromorphide was first obtained by Schryver and Lees by the action of phosphorus trichloride upon dry morphine. It is described as occurring in colourless crystals, soluble in chloroform and methyl alcohol, and melting with decomposition at 190° C.

$\beta$ -chloromorphide was prepared by Ach and Steinbock by the action of fuming hydrochloric acid on morphine at 65° C. in closed vessels. According to the authors, it forms

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Schryver-Lees, Proceedings of the Chemical Society 1900, Vol. 16, p. 143. — Journal of the Chemical Society 1900, Vol. 77, p. 1024.  
Ach-Steinbock, Berichte der chemischen Gesellschaft Berlin 1907, Vol. 40, p. 4282.

colourless crystals, melting at 188° C., soluble in ether, alcohol and benzol.

According to Ach, the two products may be distinguished by treating them with sulphuric acid. If 6.5 grammes of  $\beta$ -chloromorphide are added to 25 grammes of concentrated sulphuric acid and gently warmed on a water-bath until solution is effected, and the solution thus obtained is poured into 250 grammes of cold water, the sulpho-compound of  $\beta$ -chloromorphide will separate out in colourless prisms, which are soluble in aqueous ammonia, alkalies and acids, but not in the ordinary organic solvents.  $\alpha$ -chloromorphide, under the same conditions, gives no sulpho-derivative.

As the preparation of  $\beta$ -chloromorphide is similar to that of apomorphine, it is possible that in the preparation of apomorphine  $\beta$ -chloromorphide may be formed at the same time. Indeed, Harnack has shown that there was an apomorphine hydrochloride on the market which consisted chiefly of chloromorphide. In their pharmacological tests of  $\beta$ -chloromorphide, Harnack and Hildebrandt found that its action was considerably stronger than that of morphine, but that its fatal dose was considerably larger than that of the energetically acting dose. In contradistinction to apomorphine, it does not excite vomiting, but rather inhibits it to a certain extent. When given to frogs it displayed the characteristic action of morphine. In warm-blooded animals its employment gave rise to respiratory disturbances, but they were not of a serious nature.

G. Grund tried the use of chloromorphide in man, giving subcutaneous injections of 0.001 to 0.01 gramme ( $\frac{1}{64}$  to  $\frac{1}{6}$  grain) of  $\alpha$  or  $\beta$ -chloromorphide in suitable cases. He came to the following conclusions: Chloromorphide has a narcotic action in man which is less effective than that of morphine, or at any rate is not more powerful than the latter. Besides, in predisposed cases, respiratory disturbances occur, which may give rise to grave anxiety. The drug is therefore unsuited for therapeutic employment in man. The author thinks that cases of poisoning accompanied by respiratory disturbances, which have been reported by others after using

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Harnack, Compare Merck's Report 1910, p. 99.

Harnack-Hildebrandt, Archiv für experimentelle Pathologie, Vol. 65, p. 38.

Grund, Münchener medizinische Wochenschrift 1911, p. 1007.

apomorphine, may have been due to the chloromorphide contained in the apomorphine.

### **Chlorophyll.**

A 5 p.c. alcoholic solution of chlorophyll free from fat has recently been recommended by I. Boas as a microscopic test for the presence of fat. If a drop of chlorophyll solution is added to fæces or stomach contents which are to be tested for fat, the droplets of fat will be seen, when viewed under a low magnification, to be coloured an intense green, whereas needles of fatty acid remain unstained. In comparative experiments the author found that the chlorophyll stain was superior to the Soudan red stain formerly used for this purpose as regards distinctness and sharpness. Benda has determined the limits within which a chlorophyll solution may be employed in histological work. According to him, chlorophyll shows several advantages as a stain over Soudan red and scarlet red, especially for contrast stains. One advantage is that less care is necessary in subsequent washings and that the stain is therefore more durable. Further, the author has noticed that the subcutaneous fatty tissue and the fat of fatty infiltration are very faintly stained by chlorophyll and intensely so with Soudan red, whereas the fat of fatty degeneration is apparently more intensely stained by chlorophyll than by Soudan red. If these observations are confirmed by further investigations, there will be a prospect of finding this stain useful for diagnostic purposes. In any case it is very useful in all comparative staining methods with Soudan red and scarlet red.

### **Choline and Neurine.**

The question as to the toxicity of choline and its physiological action has, according to J. Pal, not yet been definitely settled; many contradictory statements on this subject are to be found in the literature on choline, depending perhaps upon the ease with which choline decomposes, or upon the fact that several choline bodies exist. In order to solve the question, the author employed the synthetically

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Boas, Berliner klinische Wochenschrift 1911, p. 1282.

Benda, Berliner klinische Wochenschrift 1911, p. 1246.

Pal, Zeitschrift für experimentelle Pathologie und Therapie 1911, Vol. 9, No. 2, p. 192.

prepared choline hydrochloride, which is more stable than the free base. In his experiments on cats he came to the following conclusions: Even though choline hydrochloride is a stable substance, yet its action is unequal. When given intravenously it has a depressant action, but is also capable of raising blood pressure. The latter effect may be absent after prolonged ether anæsthesia, and after the use of certain kinds of curare. In lightly anæsthetised animals, and after the division of the oblongata, the pressor effect on the blood pressure is predominant. Choline has a stimulating action on the vagus endings in the heart, but it is inconstant as it depends upon the susceptibility of the animal. "Choline acts as a stimulant on the motor centres of the brain and spinal cord and gives rise to clonic convulsions, and also upon the motor endings in the muscles, and abolishes the action of curare. The resuscitating action of curare is only transitory, for although spontaneous respiration sets in, it is arrested by paralysis of the respiratory centre. The paralysis occasioned by small doses is transitory and can be overcome by artificial respiration. — Choline excites the secretion of the lachrymal and the salivary glands by direct peripheral action. — The action on the secretion of urine and probably also that on the pancreatic secretion is an indirect one. The gut also is indirectly influenced through the circulatory system, at any rate the latter is connected with the increase in the intestinal movements." — Pal found the choline hydrochloride used by him for subcutaneous injection to be but slightly toxic.

With regard to the action of choline on the blood pressure\*), reference may be made to the communications of Popielski and Klotz. L. Popielski does not consider the choline of commerce to be sufficiently pure to give accurate results. He therefore purified it by forming its double salt with platinum chloride, which crystallises well, and found that in this way a pure product was obtained which produces a rise of blood pressure. Thus the author arrives at the same result as Modrakowski, namely that the action of choline in producing a fall in the blood pressure, which has been observed by others, is solely due to the presence of

\*) Compare Merck's Report 1910.

Popielski, Zeitschrift für physiologische Chemie 1911, Vol. 70, p. 250.

Modrakowski, Pflügers Archiv 1908, Vol. 124, p. 601.

impurities in the choline of commerce. But the rise in blood pressure caused by choline is, according to the author, only transitory. R. Klotz, on the other hand, in experiments on animals to test the action of pituitrin in raising the blood pressure, used choline in order to obtain an experimental fall of blood pressure. For this purpose he made 3 injections each of 0.0125 gramme of choline into a rabbit anæsthetised with urethane, with the result that the blood pressure gradually fell from 78 mm. of Hg. to 28 mm. As the author does not state which kind of choline he used for his experiments, his results cannot be compared with those of Popielski.

On the other hand E. Abderhalden and F. Müller, in opposition to Popielski's point of view, maintain that the occasional rise of blood pressure observed to follow the use of choline is due to the dosage of the preparation and to the method of anæsthesia adopted, and not to any impurities present in the choline employed.

Neurine hydrochloride acts in a similar way to choline in cats, but its action on intravenous injection is more powerful, and, as regards the vessels, the effect of raising the blood pressure predominates. It also temporarily abolishes the action of curare. — The muscarine-like action on the heart is inconstant and like that of choline dependent upon the experimental conditions. — Very small intravenous doses often cause a slight reduction of pressure without consequent rise of pressure; with larger doses the reduction of pressure is transitory. — Subcutaneously, neurine hydrochloride raises the pressure with subsequent continuous variations.

### Chrysarobin.

Hengst used chrysarobin successfully in combination with tar and esterdermasan\*) for the treatment of chronic eczema in veterinary practice. He prescribed a mixture of 10 grammes ( $\frac{1}{3}$  oz) of tar, 5 grammes (90 min.) of liquor carbon. deterg. and 85 grammes ( $2\frac{5}{8}$  oz) of esterdermasan, and likewise a mixture of 10 grammes ( $\frac{1}{3}$  oz) of chrysarobin with 90 grammes (3 oz) of dermasan, or a mixture of 10

Klotz, Archiv für experimentelle Pathologie 1911, Vol. 65, p. 356.  
Abderhalden-Müller, Sitzung der physiologischen Gesellschaft Berlin, July 21, 1911.

Hengst, Berliner tierärztliche Wochenschrift 1911, p. 360.

\*) Merck's Reports 1903 and 1906.

grammes ( $\frac{1}{3}$  oz) of chrysarobin with 90 grammes (3 oz) of tar-dermasan, of which the last named mixture, the tar-chrysarobin-dermasan, is said to have the most lasting action. These mixtures are not suitable for the treatment of moist eczema. In dry chronic eczema and dermatitis the ointment is rubbed into the skin, previously shaved and cleansed, for 3 to 5 minutes 2 to 3 times a day, and the part is then covered over with cotton wool. All the cases treated with this preparation, even those which had been previously unsuccessfully treated with other ointments, healed in 1 to 3 weeks by this form of treatment.

### Cinnamic Allyl Ester.

Cinnamic allyl ester,  $C_6H_5 \cdot CH:CH \cdot CO \cdot O \cdot C_3H_7$ , is a colourless liquid, miscible with alcohol and fats, boiling at about  $180^\circ C$ . under diminished pressure.

Starting from the fact that drugs containing cinnamic acid, as for example balsam of Peru and hetol, have on many occasions been used with excellent results in tuberculous processes, E. Blos carried out experiments with cinnamic acid allyl ester. The author considers tuberculous abdominal fistulæ and tuberculous fistulæ following upon operations on the adnexa to be especially suited for treatment with this preparation. In order to obtain the most satisfactory action of the drug, it should come into contact with the base of the fistula; in simple fistulæ it should be applied on tampons and in branched fistulæ, mixed with Beck's bismuth paste, for which purpose the author used a mixture of cinnamic allyl ester (1 to 20 p.c.) and bismuth paste\*). The fistulæ were re-filled with this mixture every 1 to 2 weeks.

The favourable influence of the cinnamic acid component of the ester on tuberculous processes can scarcely be doubted in the light of the now recognised action of other cinnamic acid derivatives in tuberculosis; the only question is, whether the allyl component also has a curative action, seeing that allyl derivatives are usually reckoned among the bodies which act as local irritants.

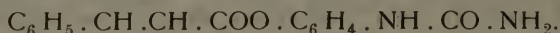
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Blos, Versammlung deutscher Naturforscher und Ärzte, Karlsruhe, September 1911. — Klinisch-therapeutische Wochenschrift 1911, p. 1240.

\*) Compare p. 173.

**Cinnamoyl-Para-Oxyphenyl Urea.**

This preparation, which is marketed in the form of tablets under the name of "Elbon", forms light, white, odourless and tasteless needles, melting at 204° C., and corresponding to the chemical formula



The preparation is only slightly soluble in water, somewhat more readily soluble in alcohol, acetone and fatty oils. Its solubility in fats insures its ready absorption in the system. It soon appears in the urine as benzoic acid and hippuric acid, the oxidation products of cinnamoyl-para-oxyphenyl urea. In the organism elbon is decomposed into cinnamic acid or benzoic acid and a derivative of para-oxyphenyl-urea, which contains the para-aminophenol group. Both products possess antizymotic and antipyretic properties, and when given in suitable doses to phthisical patients, they lead to a steady and lasting remission of fever, without giving rise to unpleasant by-effects, coupled with a pronounced feeling of well-being, and an improvement in the quality of the sputum and a diminution in the pulmonary secretion.

According to W. Minnich, cinnamoyl-para-oxyphenyl urea is a useful drug in the treatment of phthisis, and has for some years been successfully employed in a number of cases for the prolonged treatment of tuberculous pyrexia, for the purpose of husbanding the strength and rapidly procuring remission. It is, in his opinion, capable of partially replacing creosote. Its occasional failure is not surprising, when the polymorphous character of tuberculous pyrexia is taken into consideration, and should not interfere with its employment.

Elbon is administered in doses of 3 to 4 grammes (45—60 grains), which are gradually reduced (one gramme every 3 hours, beginning at 9 a. m.) in most cases with sub-febrile and medium temperatures in the formative and reparative stages, and also in the pyrexia of the ulcerative end-stages. The drug failed in massive infections coupled with high fever, in which the modern antipyretics are also useless, and also in a number of purely infective pyrexias, especially in closed areas of the parenchyma of the lungs and of the lymphatic glands.

**Cobalt Chloride.**

Cobalt chloride,  $\text{Co Cl}_2 + 6\text{H}_2\text{O}$ , forms red crystals, soluble in water and alcohol.

A sensitive test for hydrogen peroxide is obtained, according to M. Leuchter, by mixing a 1 p.c. aqueous solution of cobalt chloride with an equal volume of a solution of 1.6 grammes of borax in 100 grammes of water and 20 grammes of glycerin. 1 to 2 c.c. of this reagent are poured into a narrow test-tube and an equal volume of the liquid to be tested is "layered" on to the surface. Should it contain hydrogen peroxide, a brownish to blackish-brown ring is formed at the junction of the two liquids; it will appear immediately or in a short time, according to the amount of  $\text{H}_2\text{O}_2$  present, and at the same time the formation of gas may be observed. It is said that this reaction is plainly visible if only 1 c.c. be used of a mixture of 1 drop of hydrogen peroxide (3 p.c.) in 100 c.c. of water. Sodium perborate also gives this reaction, but persulphates only gives it on warming, or on the addition of solution of caustic soda. The reaction can therefore also be used to distinguish between perborates and persulphates.

**Cocaine Hydrochloride.**

In a paper dealing with the nature and treatment of the nervous vomiting of babies, F. Rott reports upon the value of cocaine and arrives at the following conclusions.

In purely nervous, spastic vomiting, the cause of which is to be sought in the hyperæsthesia of the gastric mucous membrane, the therapeutic use of cocaine is highly successful, if the employment of a fat-free diet does not lead to a cure. In these cases he administered 10 c.c. ( $\frac{1}{3}$  oz) of a 0.01 p.c. solution of cocaine hydrochloride 5 times a day 10 minutes before meals, viz., 0.001 gramme ( $\frac{1}{64}$  grain) for a dose, and 0.005 gramme ( $\frac{1}{12}$  grain) in the course of the day. This treatment led to the complete cessation of vomiting in the course of 3 days; only in one case, after the cocaine had been discontinued for 4 days, vomiting occurred 3 times in one day. After the inhibition of the vomiting the author usually continued the cocaine medication for 6 days longer. At first he tried the use of larger doses, in one case, for

Leuchter, Chemiker-Zeitung 1911, p. 1111.

Rott, Therapeutische Monatshefte 1911, p. 525.

example, giving 0.005 gramme ( $\frac{1}{12}$  grain) 3 times a day, but they gave rise to attacks of sweating, whereupon he returned to the doses mentioned above, which had the same action on the vomiting as the large doses. In no case did the author observe other toxic symptoms following the administration of cocaine. He mentions another favourable by-effect of cocaine, viz., its general sedative effect on the babies. On the other hand, in cases of uncontrollable vomiting accompanied by general flaccidity of the muscles and evidently due to gastric atony Rott was unable to obtain a favourable effect with cocaine. In pyloric spasm, also, the author hopes to achieve a success by the use of cocaine, as his experiences have so far proved satisfactory.

A new method of treating essential pruritus vulvæ and other sacral neuroses has been described by G. Schubert. It consists in the epidural injection of the following solution in the direction of the sacral canal:

Rp. Cocain. hydrochl.	0.1 gramme ( $\frac{1}{2}$ grains)
β-Eucain.	0.1 gramme ( $\frac{1}{2}$ grains)
Sod. chlor.	0.4 gramme (6 grains)
Aq.	200.0 gramme ( $\frac{6}{3}$ oz)

In the beginning the author injects 1.5 c. c. (25 min.) and later 3 to 5 c. c. (50—85 min.).

A combination of cocaine, alypin and adrenalin, known under the name of "orthonal", is recommended by B. Moses as an anæsthetic. He bases this recommendation on the experiences of recent years which show that several anæsthetics given together in small doses act better than a large dose of a single anæsthetic, and that a combination of this description has a less toxic effect. It is said to be useful in minor surgery and in dentistry, when given subcutaneously.

As an analytical test for cocaine, E. H. Hankin modified the well known potassium permanganate reaction in the following manner. A drop of concentrated potassium permanganate solution is allowed to dry on a slide and a drop of a very weak solution of cocaine in a saturated aqueous solution of alum is added. In about 1 to 2 minutes the formation of small, red plates may be observed, which can be easily distinguished from the permanganate com-

Schubert, Münchener medizinische Wochenschrift 1911, p. 745.

Moses, Deutsche medizinische Wochenschrift 1911, p. 2138.

Hankin, The Analyst 1911, p. 2. — Apothekerzeitung 1911, p. 456.

pounds of other anæsthetics, such as tropacocaine, eucaine, stovaine, novocaine, etc. F. J. Seiter and F. Enger suggest as a microscopic test for cocaine and other anæsthetics the preparation of the crystalline forms of these substances with gold chloride, platinum chloride, chromic acid, and potassium permanganate.

### **Collodion.**

A useful, simple method of treating furunculosis is described by W. Fuchs. It consists in surrounding the area of inflammation with a "collodion ring", which stimulates the process and prevents the infection from spreading. For this purpose a collodion ring is painted round the furuncle by means of a brush; the ring varies according to the size of the swelling, but should enclose a free space at least 2 cm. ( $\frac{3}{4}$  in.) in diameter. The collodion ring is renewed several times a day; the inner part, which is free from collodion, is kept the same size, while the ring is gradually extended outwards. The pressure exerted by the collodion ring on the centre forces the tip of the furuncle outwards and the inflammatory process is made to advance centripetally. This treatment at the same time hastens maturation of the boil, so that in the course of 1 to 3 days the tip of the furuncle bursts and the central core is forced out. Fuchs recommends this method for further investigation.

For the treatment of chilblains, urticaria and ulerythema centrifugum, P. Unna recommends a preparation of collodion consisting of one part of soft soap and 5 parts of collodion. It is said to form an excellent preparation for use as "pressure collodion". In circumscribed dermatitis, leading to an exuberant growth of horny skin, especially for scaling psoriasis, eczema and lichen, the author uses a "scaling-collodion", viz., collodion containing 10 p.c. of salicylic acid and anæsthesine, which a few days after its application causes the skin of the part treated to peel off, leaving a smooth surface.

### **Copper Sulphate.**

A soft chancre in the male urethra, the diagnosis of which had been confirmed by endoscopic examination, and which

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Seiter-Enger, American Journal of Pharmacy 1911, p. 195.

Fuchs, Münchener medizinische Wochenschrift 1911, p. 1195.

Unna, Berliner klinische Wochenschrift 1911, p. 1800.

spontaneously excreted a yellowish-brown, thin fluid containing yellow fragments, without causing œdema of the prepuce or thickening of the lymphatic vessels, was treated by A. Glingar and M. Blach by dabbing the posterior part of the ulcer with a 10 p.c. copper sulphate solution. It reacted well to this treatment and became so rapidly clean, that when examined endoscopically 2 days later, already some bleeding points could be recognised. Treatment was then continued more towards its anterior part, partly with copper solution, and partly with a 10 p.c. silver nitrate solution. No marked difference was observed in the action of these two salts. The ulcer healed and the Ducrey's bacilli, which had been present in the urine, disappeared.

### Crotalin.

Crotalin is the name applied to the venom obtained from the venom-sac of the rattlesnake (*Crotalus adamanteus*) and prepared in a special manner; it is issued in an aqueous, sterile solution put up in ampoules, in different strengths. Up to the present the venom of the rattlesnake has been used for physiological experiments, and therapeutically for immunisation against snake-bite. But in the form of crotalin it is apparently destined to prove of further use in medicine. After L. E. Self a few years ago made the chance observation that an epileptic who had been bitten by a rattlesnake remained free from attacks for years, R. Spangler and afterwards Fackenheim tested the therapeutic use of crotalin in epilepsy.

Spangler reports 11 cases of epilepsy, which show that crotalin certainly has a favourable influence on the symptoms of this disease, for it not only caused an improvement in the general health, but also a diminution in the number of attacks, or their total disappearance. These results were confirmed by the investigations of Fackenheim. The author gave his patients a subcutaneous injection weekly, beginning with the weakest solution of crotalin ( $\frac{1}{200}$  grain = 0.000325 gramme) and rising in the course of several weeks to the strongest so-

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Glingar-Blach, Wiener medizinische Wochenschrift 1911, p. 2370.  
Self, Medical World 1908.

Spangler, New York Medical Journal 1910, 3<sup>rd</sup> September, and  
September 9, 1911.

Fackenheim, Münchener medizinische Wochenschrift 1911, p. 1872.

lution ( $\frac{1}{50}$  grain=0.0013 gramme). The injections are followed by rather severe local irritation accompanied by pains which may last for 3 to 4 days, so that the application of cold hydropathic compresses are occasionally necessary for their relief. Apart from pain and swelling, the author has observed no unpleasant by-effects, such as fever or pathological conditions of the urine, the digestion, the cardiac action or the respiration. The inflammatory symptoms diminish as the number of the injections and the strength of the solution increase. The best results, according to present experience, may be expected in those cases in which the disease is in an early stage and has not given rise to any changes in the cerebral cortex or the central nervous system. The employment of crotalin is quite without danger so long as the necessary measures of caution are observed and the treatment is carried out in the manner described by the author. The result of its action is then surprisingly good. Fackenheim confirmed the observation that crotalin not only had a favourable influence on the severity and number of the fits and on the irritability of the nervous system, but that the general health was improved, the intellectual capacity, the tone and the metabolism of the patients were raised in every way. Crotalin acts on the central nervous system and its excitability, and on the quality of the blood and the metabolism of the patients.

But crotalin should not be regarded as a perfectly harmless substance. If it is carelessly handled, it may become very dangerous, as is shown by a case reported from Philadelphia. A child, aged 5, was given 4 crotalin injections in the course of one week and died of the effects of the too rapidly repeated injections.

### Cycloform.

Further communications\*) concerning cycloform, which confirm its utility as a local anæsthetic, were made in the past year by E. Bircher, A. Rosenberg, H. Bosse and Th. Dendorff.

Bircher used it on his own person in the form of a 10 p.c. ointment for itching eczema, which he had contracted

\*) Compare Merck's Report 1910.

Bircher, Medizinische Klinik 1911, p. 223.

Rosenberg, Deutsche medizinische Wochenschrift 1911, p. 409.

Bosse, Zentralblatt für innere Medizin 1911, p. 593.

Dendorff, Deutsche zahnärztliche Wochenschrift, Vol. 14, No. 20.

while disinfecting his hands by means of acetone-alcohol, and states that it immediately relieved the irritation and at the same time had a favourable influence on the healing process. But this latter effect was less evident in another case. The use of a 5 p.c. cycloform ointment in relieving irritation proved also successful in obstinate prurigo, even though it did not cause healing. Cycloform is also useful in the form of an ointment or dusting powder for burns of the second and third degree, in which it relieves pain, stimulates the formation of granulations and diminishes secretion. Like Most, Bircher also obtained good results in indolent ulcers of the leg, and he found cycloform particularly useful for the after-treatment of ulcers of the leg which had been treated by the Rindfleisch-Friedel method of spiral incision; the preparation could be used after the operation as an anæsthetic when applying the bandage. The author considers cycloform to be suitable for the treatment of various forms of fæcal fistulæ. In 6 cases he applied a 10 p.c. ointment round the opening of the fistula and changed the bandage 4 to 5 times a day; in almost all the cases he was thus able to prevent the occurrence of troublesome cutaneous irritation caused by the intestinal secretions, and to abolish the pains.

Rosenberg expresses himself well satisfied with the anæsthetic properties of cycloform in tuberculous laryngitis. In his experience the insufflation of the drug in the form of powder causes no unpleasant sensations and no symptoms of intoxication. The action takes effect comparatively quickly. The patients are usually enabled to swallow without pain within the course of a few minutes to a quarter of an hour, even if severe dysphagia had been present, and analgesia often lasts for 24 hours. Bosse's results in the treatment of tuberculous laryngitis with cycloform were also satisfactory. He applied the drug in the form of cycloform-coryfin (1:20 to 25), as recommended by Baumgarten, by means of a suitable atomiser, which the patients are able to carry in their pockets.

Dependorf used cycloform in dental practice; it acts as an anæsthetic and antiseptic in painful inflammatory processes.

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Most, Merck's Report 1910, p. 154.

Baumgarten, Merck's Report 1910, p. 151.

It may be prescribed in the form of powder after minor operations, painful inflammation of the alveoli in the course of periostitis and osteitis, inflammation of the gums, marginal gingivitis, and also for tender rhagades at the corner of the mouth, small ulcers of the tongue and of the mucous membrane of the cheek, etc.

### Curd Soap.

Even though it has not yet been conclusively proved in which way sodium oleate and the curd soap recommended by Senator exert their favourable action in cholelithiasis, M. Mosse has recently again called attention to the use of "sapo medicatus"\*), as he believes that it deserves more consideration in general practice. This is also evident from the results of pharmacological trials by W. Weinberg which show that the soap has a stimulating action on the secretion of bile. The method of prescribing the soap suggested by Senator, and favourably commented on by Mosse, is as follows:

Rp. Sapon. medicat. 10—15.0 grammes ( $\frac{1}{3}$ — $\frac{1}{2}$  oz)

Mucil. acac. q. s. ut f. pil. No. 60.

Sig.: One pill to be taken 3 times daily.

### Dermatol.

The fact that bismuth preparations occasionally cause symptoms of poisoning on external use is known, at least I have already alluded to this observation. Care is especially necessary in extensive burns, if large areas have to be treated with bismuth preparations applied in the form of ointments or dusting powders, for the danger is present that considerable amounts of bismuth may be absorbed. Rössle reports 3 cases in which the intoxication following upon the use of dermatol ended fatally. These were cases of burns of the first to third degree, which had been treated with dermatol. In one of these cases a large amount of bismuth was found in the urine 4 days after the commencement of treatment,

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Mosse, Therapie der Gegenwart 1911, No. 12.

\*) The *sapo medicatus* of the German Pharmacopœia is made with sodium hydroxide, lard and olive oil.

Weinberg, Zentralblatt für Stoffwechselkrankheiten 1911, No. 1.

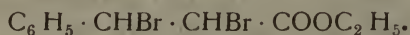
Rössle, Münchener medizinische Wochenschrift 1911, p. 279. —

Compare L. Dorn, Beiträge zur klinischen Chirurgie, Vol. 70 (Angerer-Widmungsband).

on the fifth day the mouth was coated and death took place on the ninth day, in spite of the medication having been stopped on the sixth day. Leaving off the drug soon after the appearance of symptoms of intoxication does not always prevent a fatal result, as is shown by the second case described by the author, in which, although the dermatol treatment was soon left off, the fatal termination could not be avoided. According to Rössle, the first symptom of bismuth poisoning is stomatitis. At first white patches are seen, and later a violet-black line on the gums. At the same time symptoms of irritation of the kidneys and affections of the large intestine appear, and in severe cases icterus and vomiting also occur.

### Dibromo-Cinnamic Ethyl Ester.

This preparation, which Ellinger has also named cinnamic-ester bromide or zebromal, occurs as a white, crystalline powder, melting at 74—75° C.; it is soluble in alcohol and fatty oils, but practically insoluble in water. Its chemical formula is:



To judge by the pharmacological studies of A. Ellinger and Y. Kotake, cinnamic-ester bromide would appear to be a preparation destined to replace the alkaline bromides in the treatment of epilepsy. For, according to the experiments on animals made by these authors, it meets the demands required by Wyss and Ulrich of an organic preparation of bromine really useful for therapeutic purposes: It contains a high percentage of bromine (48 p.c.), it enriches the tissues in bromine or replaces the chlorine practically to the same extent as do the bromine salts, and gives rise to no harmful by-effects. A point of practical importance in its employment is the fact that if necessary, e. g., on the appearance of symptoms of bromism, the accumulation of bromine may be reduced by increasing the intake of salt. With regard to the accumulation of bromine and the displacement of chlorine in the blood and with regard to its physiological action, cinnamic-ester dibromide has an action practically equal to

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Ellinger-Kotake, Archiv für experimentelle Pathologie 1911, Vol. 65, p. 87.

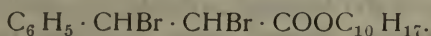
Wyss-Ulrich, Archiv für Psychiatrie und Nervenkrankheiten 1909, Vol. 46, p. 197.

that of sodium bromide, when comparing equal doses of bromine. The elimination of bromine in the urine is also similar to that of sodium bromide, but in comparison to the total amount of halogen a greater portion of bromine is excreted earlier. A small portion of the bromine appears in the urine in organic combination. A considerable amount of bromine is found in the fæces, part of which is excreted by the intestinal mucous membrane. The distribution of bromine in the organs is the same as when sodium bromide is given. The blood usually contains the highest percentage of bromine and almost without exception the highest ratio "bromine: total halogen". This ratio is greater in the blood corpuscles than in the serum. The bromine contained in the brain is entirely, or almost entirely, present in the form of ions. The liver is able to act as a bromine depot to a slight degree.

Therapeutic trials with dibromo-cinnamic ethyl ester are now being made. As soon as they are completed, I shall report on the method of administration and the dosage.

#### **Dibromo-Dihydro-Cinnamic Borneol Ester. (Adamon.)**

This preparation, in contradistinction to the esters of borneol containing bromine hitherto known and used in therapeutics, is a solid body, which can be administered in the form of tablets. It forms a white, crystalline, almost odourless and tasteless powder, having the chemical formula:



It melts at about  $75^\circ\text{C}.$ , and contains approximately 35 p. c. of bromine. It is soluble in hot alcohol, ether and chloroform, but insoluble in water\*).

Dibromo-dihydro-cinnamic borneol ester is said to be of use in nervous conditions, such as heart disease, neurasthenia, hysteria, agrypnia, and also in the disturbances of menstruation and pregnancy. The dose has been fixed at 0.5 to 1 gramme ( $7\frac{1}{2}$ —15 grains), 2 to 3 times a day. According to the pharmacological investigations which have been made, the preparation is said to be well borne and slowly undergoes decomposition in the system with liberation of inorganic bromine.

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\*) Apotheker-Zeitung 1911, p. 1057.

**Dicentrine.**

Some years ago Y. Asahina found an alkaloid in *Dicentra pusilla* Sieb. and Zucc, a Papaveraceæ (Fumaroideæ) indigenous to Japan (called in its native land "koma-kusa"); he named it dicentrine. It is most probably identical with the alkaloid found by G. Heyl in *Dicentra formosa*, as it agrees with it as regards its melting point ( $168^{\circ}$ — $169^{\circ}$  C.) and colour reactions. Its chemical formula,  $C_{20}H_{21}NO_4$ , shows it to be isomeric with papaverine, hydroberberine, and canadine. Pure dicentrine forms almost colourless prisms, insoluble in water, soluble in alcohol and chloroform. It cannot yet be obtained in the market.

The pharmacological investigation of dicentrine was carried out by K. Iwakawa. For his experiments on frogs, mice, rabbits and dogs he used an aqueous solution of dicentrine acetate neutralised with sodium carbonate. Frogs were given doses of 0.004 to 0.01 gramme, mice, 0.003 to 0.01 gramme, rabbits per kilogramme 0.04 or 0.1 gramme in two doses of 0.04 and 0.06 gramme, and a small dog 0.5 gramme per kilogramme.

As is the case with most opium alkaloids, when small doses of dicentrine are injected subcutaneously or intravenously into frogs and warm-blooded animals, light narcosis is produced. Medium doses cause a condition of spasm, which in frogs merely depends upon irritation of the centre for spasm in the medulla. This distinguishes dicentrine from its homologue, bulbocapnine. In warm-blooded animals the convulsions which take place probably depend upon a centre situated higher than the spinal cord, as is the case with several homologues of morphine. In testing the reflexes, it was found that the spinal cord of the frog gradually loses its excitability until this is totally abolished. Further, dicentrine causes weakening of the general reactive capacity of the frog's heart until it stops beating, which depends upon the paralysis of the motor mechanism. In warm-blooded animals the heart is also injured and the vascular centre is paralysed. This distinguishes dicentrine from other poisons which give rise to convulsions, such as camphor and morpho-oxy-acetic ester. In large doses

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Asahina, Archiv der Pharmazie 1909, Vol. 247, p. 206.

Heyl, Archiv der Pharmazie 1903, Vol. 241, p. 313.

Iwakawa, Archiv für experimentelle Pathologie 1911, Vol. 64, p. 369.

dicentrine paralyses the respiratory centre. In warm-blooded animals the paralysis is preceded by transient stimulation of the centre; this phase is absent in cold-blooded animals.

### Digitalis Preparations.

*Folia digitalis.* In cardiac insufficiency and disturbances of compensation, A. Mayor is in favour of interrupted or continuous treatment with digitalis; he recommends small doses of digitalis and the treatment should be begun immediately after the first attack of asystole. The object is to prevent or delay further attacks. If the interrupted method of treatment be chosen, then every week or ten days powdered digitalis leaves are given for the first 3 days in such quantity that 1 gramme (15 grains) is administered during the course of a month (if digitoxin is used 0.001 gramme ( $\frac{1}{64}$  grain) will be required for this period). But should the disease advance and these doses prove insufficient, they should not be increased but should rather be given for a greater number of days. In this way the continuous method of treatment may eventually be reached. As a daily dose 0.1 gramme ( $\frac{1}{2}$  grains) of digitalis powder may be recommended, consideration being given to the fact that it acts individually, e. g., it may be insufficient for one patient, while it causes cumulative symptoms in another. Should the dose prove insufficient, it must in time be increased, not because the patient has become accustomed to it, but because the advance of the disease renders this measure necessary. Cases naturally exist in which the continuous method of treatment with digitalis is advisable without a preceding interrupted treatment, e. g., in essential hypertrophy with great dilatation, pericardial adhesions, aortic insufficiency and complications (chronic bronchitis, pleural adhesions, extensive sclerosis of the lung with bronchorrhœa). Besides digitalis leaves, Mayor recommends as an adjunct to this treatment the use of hydrastis, according to the following prescription:

Rp. Ext. digital.	4.0 grammes (60 grains)
Ext. hydrast. Canad.	4.0 grammes (60 grains)
Glycerin.	2.0 grammes (25 min.)

M. Sig.: 10 drops to be taken at a specified time, before going to bed.

A. Petit also recommends small doses of digitalis for asystole consequent upon mitral stenosis. Daily doses of 5 to 10 drops of digitalis tincture (for a period of 4 to 5 days) may be given at first, and if the dose be well borne it may be increased on the return of an attack. The author does not consider the occurrence of hæmoptysis following upon digitalis medication to be a contra-indication to the use of digitalis, as it may occur with the greatest care and the smallest doses and usually passes off rapidly.

Focke has observed that pulmonary hæmorrhage is favourably influenced by digitalis medication, and suggests the treatment of hæmoptysis with digitalis. The author has previously reported upon the use of digitalis in the treatment of epistaxis\*). In pulmonary hæmorrhage he recommends the following prescriptions for adults:

Rp. Infus. digital. fol. titr. 0.8—1.0:145.0 grammes  
(12—15 grains to 5 oz)

Spirit. 5.0 grammes (80 min.)

M. Sig.: One tablespoonful to be taken after meals, until the whole of the mixture has been used up.

Rp. Digitalysat. (Bürger) 15.0 grammes ( $\frac{1}{2}$  oz)

Sig.: 15 drops to be taken after meals 4 times daily for 2 days, on the third day only 3 times a day.  
(If the hæmorrhage be still present, 20 to 30 drops may be given once for the first dose.)

If there be much coughing, the author adds a narcotic to the infusion, for example 0.05 gramme ( $\frac{3}{4}$  grain) of morphine hydrochloride, or 0.1 gramme ( $\frac{1}{2}$  grains) of codeine phosphate. According to Focke, no drug has such a rapid and permanent action as digitalis.

A. Hecht also obtained a good effect from the use of digitalis in combination with ergotin in 2 cases of pulmonary hæmorrhage (in acute articular rheumatism, mitral insufficiency, anasarca with considerable ascites). He prescribes a modification of Huchard's pills:

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Petit, Progrès médicale 1911, No. 9.

Focke, Therapie der Gegenwart 1911, p. 396.

\*) Compare Merck's Report 1910, p. 157.

Hecht, Therapie der Gegenwart 1911, p. 139.

Rp. Fol. digit. pulv. titr.	1.0—2.5 grammes (15—40 grains)
Ergotin.	2.5 grammes (40 grains)
Scillæ	3.0 grammes (45 grains)
Calomel.	0.5 grammes ( $7\frac{1}{2}$ grains)

M. Ft. pil. No. 50. Sig.: 2 pills to be taken 3 times daily.

These pills are also said to be highly effective in dropsy, even in those cases which do not react well to digitalis in combination with modern diuretics. The author explains this by the action of the ergotin, which counteracts the vaso-constrictive action of the digitalis and especially causes the dilatation of the smallest renal vessels.

With regard to the difference of opinion as to the value of digitalis in typhoid, the paper by A. Skutetzky is of special interest. Having had an abundance of cases under treatment, the author expresses himself in favour of the use of digitalis. In his experience it has a favourable effect, occasionally even a life-saving influence, on the heart, which has been severely affected by the typhoid infection; wherefore its use is indicated under all circumstances on the appearance of cardiac weakness in the course of typhoid fever. Its administration varies according to the individuality of the patient. According to the age, general condition and severity of the symptoms a daily dose of 0.5 or 1.0 gramme ( $7\frac{1}{2}$ —15 grains) is given at first, and this dose is diminished by 0.1 gramme ( $1\frac{1}{2}$  grains) day by day until a daily dose of 0.1 or 0.05 gramme ( $1\frac{1}{2}$ — $\frac{3}{4}$  grain) is reached. If the action takes place earlier, further treatment may be discontinued. In severe cases, in order to increase the action, the suggestion of von Jacksch may be followed, and 20 drops of ether may be added to the infusion of digitalis. The occurrence of intestinal hæmorrhage constitutes no absolute contra-indication to digitalis treatment; but in older patients a certain amount of caution in the dosage is necessary, for in the presence of cardiac insufficiency the digitalis might possibly give rise to renewed hæmorrhage. In severe collapse, in order to hasten the commencement of the action, Skutetzky prefers the use of camphor, ether, strophanthus, caffeine and saline infusion, and under certain conditions, adrenalin. Should cumulative symptoms be observed during the administration of digitalis, the treatment must be interrupted.

In acute œdematous beri-beri E. Mesley obtained good results with daily doses of 5 to 10 grammes (85 min.— $\frac{1}{3}$  oz) of tincture of digitalis. In one case he gave altogether 60 to 70 c.c. ( $2\frac{1}{3}$  oz), and achieved a rapid and permanent cure.

General communications regarding digitalis treatment and the position of the biological tests of the digitalis substances have been made by Th. Brugsch, E. Edens, R. Gottlieb, A. Bickel, E. Schmoll, W. Hale, T. C. Githens and Focke. As these do not lend themselves to short abstractions, reference should be made to the original papers.

Digitalis Winckel. As in the process of drying the digitalis leaves part of the active substance is destroyed in consequence of the action of enzymes, and bodies are formed which give rise to harmful by-effects, M. Winckel has worked out a method of conservation which does away with these drawbacks. The preparation is placed on the market in the form of tablets of 0.05 gramme ( $\frac{3}{4}$  grain) of folia digitalis. According to H. Ehlers, its action always remains the same and it gives rise to no digestive troubles. Its indications and dosage are the same as for digitalis.

Digalen. A case reported by A. Montandon proves how risky it is to assert that any preparation of digitalis is entirely free from cumulative action; on account of this case he arrived at the following conclusions with regard to digalen: Digalen is a drug which is extremely well borne and which displays its full action on the cardiac muscle even after prolonged use. But it is not free from cumulative action, as was at first generally believed to be the case. In the case

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Mesley, *Presse médicale* 1910, p. 720.

Brugsch, *Medizinische Klinik* 1911, p. 24.

Edens, *Therapeutische Monatshefte* 1911, p. 1.

Gottlieb, *Therapeutische Monatshefte* 1911, p. 9.

Bickel, *Medizinische Klinik* 1911, p. 333.

Schmoll, *American Journal of the Medical Sciences* 1911, January.

Hale, *American Journal of Pharmacy* 1911, p. 97.

Githens, *Journal of the American Medical Association* 1911, p. 606.

Focke, *Therapeutische Monatshefte* 1911, p. 533.

Winckel, *Münchener medizinische Wochenschrift* 1911, p. 575.

Ehlers, *Münchener medizinische Wochenschrift* 1911, p. 575.

Montandon, *Revue médicale de la Suisse romande* 1910, No. 4.

— *Deutsche medizinische Wochenschrift* 1911, p. 321.

described in detail by the author the cumulative action of digalen showed itself in the following series of symptoms: Great retardation and weakening of the pulse, arrhythmia, general asthenia, dimness of vision, chloropsia. Umber had already pointed out that digalen was not free from cumulative action. Müller confirmed this, and F. Heydner also observed, after the prolonged administration of small doses of digalen, loss of appetite, vomiting and irregular cardiac action, so that the further administration of the drug had to be discontinued. The author also reports a case of severe digalen poisoning and he considers that more attention should be paid to the exact dosage. He also gives instructions for the treatment of any by-effects which may occur.

Pagliano, who has used the drug with good effect in various cardiac affections and especially in myocarditis, recommends it on account of its beneficial action on the heart and on diuresis. In his experience its intramuscular injection is well borne.

**Digitalis Gelatin** (gelina digitalis). In order to avoid the well known disadvantages of digitalis leaves, M. Herz prepared a digitalis preparation by macerating the drug with liquid gelatin and giving it a form suitable for administration. He states, as a result of his therapeutic experiments, that this preparation not only displays the full action of digitalis, but it also does not cause gastric or intestinal irritation. It cannot be expected that the final stage has been reached in the experiments for preparing digitalis preparations which are effective, uniform in action and at the same time harmless, for quite recently a new digitalis preparation has been recommended, the so-called

**Digitalyl.** It is to a certain extent introduced into therapeutics as a substitute for infusion of digitalis, but is said to have the additional advantage of being a uniform compound, which keeps well and has a uniform action. According to Kantorowicz, it is extracted from digitalis leaves by

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Umber, Merck's Report 1906, p. 88.

Müller, Münchener medizinische Wochenschrift 1909, p. 904.

Heydner, Münchener medizinische Wochenschrift 1911, p. 1511.

Pagliano, Gazette des hôpitaux 1911, No. 92.

Herz, Wiener klinische Wochenschrift 1911, p. 821.

Kantorowicz, Berliner klinische Wochenschrift 1911, p. 1804.

means of superheated steam and forms a fluid extract, which in 10 grammes contains the active components present in an infusion of digitalis of 1 in 100. It is administered in the form of drops, in doses of 20 drops given every two hours. When its full action has been attained, which according to the author occurs on an average in 48 hours, half the dose (10 drops) may be given for one more day, a careful watch being kept on the pulse rate and the pulse rhythm. The drug has, in the author's opinion, proved successful and is said never to have given rise to gastric disturbances or cumulative action. Kantorowicz considers that the biological tests of the value of the digitalis preparations, which have been advanced in the last few years, more especially by the work of Focke, do not form an ideal method of examination; he believes that chemical tests would be more satisfactory, as the analytical balance is more reliable than the calculation by frog units.

Digipuratum was described in detail by R. Gottlieb and R. Tambach with regard to its preparation, physiological tests, therapeutic effects and compatibility, and the authors called special attention to the energetic action of the drug and the relatively slight disturbances caused by it in the stomach and intestines. Hale investigated its pharmacological action by giving intravenous injections to cats and established the fact that it immediately diminished the pulse rate and raises the blood pressure. Within 2 minutes the pulse rate dropped from 200 to 160, and the blood pressure rose in the same time from 110 to 146. W. F. Boos, L. H. Newburgh, H. K. Marks, Linke, O. Hensel, E. Böcher, Braitmaier and J. T. Moore have reported upon the therapeutical value of the drug. The first three of

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Gottlieb - Tambach, Münchener medizinische Wochenschrift 1911, p. 10.

Hale, Hygienic Laboratory-Bulletin 1911, No. 74.

Boos, Newburgh, Marks, Archives of internal Medicine 1911, No. 4.

Linke, Therapeutische Neuheiten 1910, December.

Hensel, American Medicine 1910, November.

Böcher, Ugeskrift for Laeger 1911, No. 31.

Braitmaier, Deutsche medizinische Wochenschrift 1911, No. 51.

Moore, Journal of the State Medical Association 1910, No. 21.

these authors treated over 180 cases of primary or secondary heart disease in the course of a year. In loss of compensation they administered large doses in a short time and show the action of digipuratum graphically. They report further that the preparation displayed a prompt diuretic action and never gave rise to vomiting or diarrhoea, nor caused cumulative symptoms; on the other hand, the vomiting of individual patients suffering from heart disease is said to have been most favourably influenced by the drug. Even after the use of 106 digipuratum tablets in the course of 6 weeks for a 16-year-old patient, they observed no sign of digitalis poisoning. In their experience the preparation shows only a slight tendency to produce cumulative action, though it is not free from it. One case is especially worthy of notice; a woman, apparently moribund, came under treatment. She reacted very rapidly to digipuratum and in a week compensation was re-established. At first she was given 2 tablets daily, and this dose was continued for months; then the dose was gradually reduced and after a year the patient only required 4 to 5 tablets a week, and was even able to do without digipuratum for 8 to 10 days at a time.

If on using digipuratum it be desired to eliminate its vaso-constrictive action, it should, according to Hensel, be combined with diuretin. The following prescription has proved effective in coronary sclerosis with a tendency to angina pectoris:

Rp. Digipurat.	0.10 gramme ( $1\frac{1}{2}$ grains)
Sod. nitros.	0.12 gramme (2 grains)
M. F. pulv. Sig.:	One powder to be taken 3 times daily; or
Rp. Digipurat.	0.1 gramme ( $1\frac{1}{2}$ grains)
Diuretin.	0.6 gramme (10 grains)
M. F. pulv. Sig.:	One powder to be taken 3 times daily.

For the treatment of dyspnoea with failing diuresis the following prescription is used:

Rp. Dionin.	0.015—0.03 gramme ( $\frac{1}{4}$ — $\frac{1}{2}$ grain)
Digipurat.	0.1 gramme ( $1\frac{1}{2}$ grains)
Diuretin.	1.0 gramme (15 grains)
Mist. F. pulv. Sig.:	One powder 3 times a day.

Lincke, Böcher and Moore have also expressed themselves favourably with regard to digipuratum.

For subcutaneous use a special preparation, digipuratum solubile, is on the market, which is supplied in ampoules of 1 c.c. = 0.1 gramme of digipuratum. As the subcutaneous injection of the drug is painful, C. Rose prefers its intragluteal or intravenous application, especially in those cases in which irritation of the stomach should be avoided, or in which as speedy an action as possible is desired. In cardiac insufficiency of various origin, the author has injected 1 c.c. 1 to 3 times daily, and has obtained with it the same result as with digalen. The prolonged administration of the injections gives rise to cumulative action, as is the case with all digitalis preparations; the author observed no other unpleasant by-effects after the intravenous injection of the drug. Massalongo and Gosfarisic also express a favourable opinion as to the value of the subcutaneous injection of the drug.

### Dionin.

Wolffberg reports a case of hæmorrhagic glaucoma in which dionin proved of great service. The case was a severe one, showing slight œdema of the lids, extensive ciliary injection, marked prominence of the perforating ciliary vessels, dull steamy cornea and loss of vision, except for the power of distinguishing the light from a candle in the external visual field. After aspirin had been taken internally and a 0.5 p.c. eserine solution had been applied locally without alleviating the pain, the author resorted to treatment with dionin; he introduced the dionin in the form of powder with a little vaseline into the conjunctival sac by means of a small glass rod in the usual way, and covered it with cotton wool. Within a few minutes the pain ceased; on drawing apart the lids, which were now greatly swollen, many tears flowed forth; there was considerable chemosis of the conjunctiva bulbi, the cornea once more became clear and the pupil contracted visibly in the course of a few hours after several instillations of eserine solution had been made, though

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Rose, Berliner klinische Wochenschrift 1911, p. 2031.

Massalongo-Gosfarisic, Gazzetta degli ospedali e delle cliniche 1911, p. 95. — Klinisch-therapeutische Wochenschrift 1911, p. 1296.

Wolffberg, Wochenschrift für Therapie und Hygiene des Auges 1911, p. 103.

the contraction was slight and unequal. After a quiet, painless night the patient was able to count fingers at a distance of 2 metres with the eye which had undergone treatment. By degrees the action of the eserine became more and more effective; the media became clear, vision rose to 0.3; the pain returned once very slightly and was rapidly relieved by dionin. The author hopes that his report will encourage the trial of dionin combined with eserine in cases of hæmorrhagic glaucoma. The employment of dionin has been discouraged in the presence of sclerosis of the retinal vessels, whether rightly so the author doubts; in any case he sees no reason to extend this warning to hæmorrhagic glaucoma, even should sclerosis of the retinal vessels be present. The author has also obtained good results from the use of dionin and eserine in acute glaucoma.

A further case showing the action of dionin on the eye is of special interest in that it deals with the observations of a medical man upon himself; it is the case described by Orth. The author, who was suffering from catarrhal ophthalmia and herpes of the cornea, or from a recurrence, to which later slight iridocyclitis was added, treated his eye affection by means of dionin, which led to a rapid cure. He himself says: "Maximum dionin ophthalmia did not occur in my case, but its degree was decidedly above the average. I found the application both comfortable and pleasant. The burning sensation which follows its introduction, although severe, is quite bearable. In a few minutes there is complete euphoria. The eye affected by iritis, and in which the sudden attempts at contraction of the iris brought about by lighting a lamp in the evening cause a considerable amount of pain, is enabled by the use of dionin to look directly into the flame without the least pain. If a little more than a trace of dionin be introduced into the eye enough is absorbed to produce sound sleep. The next morning most of the ophthalmia has disappeared, and the analgesic action also. I was able to use dionin twice a week without diminution of its action, and continued the treatment for two months."

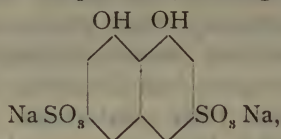
The action on the iritis manifested itself in the disappearance of ciliary injection after the second application and in

a considerable shortening of the period of illness. Dionin was also helpful in the cure of keratitis. The clearing up of the considerable cloudiness present at least led to the return of a satisfactory degree of acuity of vision. These favourable experiences gave the author the impression that dionin is one of the most effective drugs in ophthalmology, and is destined to be of great value.

The salient properties of dionin as a lymphagogue, analgesic, absorbent, irritant, antiphlogistic and local alterative are also mentioned in a publication by A. Brav. The author entirely confirms the advantages of this remedy, which have been reported by others and have been frequently described in these Reports.

### Dioxynaphthalene Disulphonic Acid.

As 1·8 dioxynaphthalene-3·6-disulphonic acid behaves as a tetrabasic acid, it forms 4 series of salts, of which two have an acid, one a neutral and one an alkaline reaction. Of these, according to P. König, the strongly acid di-sodium salt is a suitable test for chromic acid. It is a salt which crystallises in needles or platelets, having the formula



and which is readily soluble in water, yielding a pale yellow solution. The author used a  $\frac{1}{10}$  normal solution in water of the di-sodium salt as a reagent.

Aqueous solutions of chromic acid and chromates give with this reagent a permanent, light cherry-red to dark violet coloration, which is not altered by phosphoric acid. If therefore the fluid to be tested also contains iron salts, which give a grass-green coloration with the reagent, this can be eliminated by phosphoric acid. In the same way a red coloration of the reagent caused by neutral solutions of uranium or tungsten salts is removed by phosphoric acid. The chromic acid reaction is only reliable in acid solution, wherefore it is advisable to first add a few c.c. of phosphoric acid. The limit of sensitiveness of this test is reached with 0·00002 p.c.

Brav, Merck's Archives 1911, p. 174.

König, Chemiker-Zeitung 1911, p. 278.

of chromic acid, corresponding to 0.000008 p. c. of chromium. Under 0.00004 p. c. of chromic acid can be colorimetrically determined with the help of this reagent. König employed this method for the estimation of chromium in the ash of plants.

### Diphenylamin.

Diphenylamin is, as is well known, considered one of the most useful reagents in testing for nitric acid, although, like most reagents for nitric acid, it has the disadvantage of not being sufficiently positive. H. Caron has recently carried out tests with the object of establishing a diphenylamin test of the utmost sensitiveness. He found that the sensitiveness of the usual solution of diphenylamin in sulphuric acid depended upon the amount of diphenylamin used, the concentration of the sulphuric acid and the temperature. The less diphenylamin is present, the better is the reaction said to succeed. He therefore suggests the use of solutions of 0.001 to 0.005 gramme of diphenylamin in 100 c. c. of concentrated sulphuric acid, whereas Hofmann, for example, used a solution of 1:100. It is not advisable to use dilute sulphuric acid, as this diminishes the sensitiveness. The dilution, on the other hand, is said to diminish the prejudicial influence of any hydrochloric acid which may be present. If hydrochloric acid be present in the liquid to be tested, the author recommends the use of the following solution. A few milligrammes of diphenylamin are dissolved in 100 c. c. of concentrated sulphuric acid and 40 c. c. of water and 2 to 3 c. c. of  $\frac{1}{10}$  normal hydrochloric acid are added. 5 c. c. of this mixture are then added to 0.5 c. c. of the fluid to be tested. Heating hastens the appearance of the reaction and its intensity. This mixture is said to be less sensitive than the reagent prepared with concentrated sulphuric acid alone. In the presence of alcohol, ether, glycerin, phenol, salicylic acid and carbohydrates the use of the reagent containing hydrochloric acid is to be preferred.

W. A. Withers and B. J. Ray consider that the diphenylamin test should be similarly modified. They use a solution of 0.7 gramme of diphenylamin in 60 c. c. of concen-

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Caron, *Annales de chimie analytique* 1911, Vol. XVI, p. 211.

Hofmann, *Compare Merck's Reagenzien-Verzeichnis* 1908, p. 116.

Withers-Ray, *Journal of the American Chemical Society* 1911, Vol. 33, p. 708.

trated sulphuric acid and 28.8 c.c. of water, to which, when cool, 11.3 c.c. of hydrochloric acid (sp. gr. 1.19) are added. To 1 c.c. of the fluid to be tested for nitric acid, or nitrous acid, 1 drop of the reagent is added, this mixture is "layered" on to 2 c.c. of concentrated sulphuric acid and heated to 40° C. on a water-bath. By this method the presence of nitric acid is said to be detected in the proportion of 1:44 million, and nitrous acid in the proportion of 1:32 million, by the well known violet ring.

In testing water for nitric acid, Tillmans and Sutthoff are of opinion that the uncertain results which have so far been obtained are due to the fact that the water to be tested usually contains too little chloride, which is essential for the success of the reaction. They therefore suggest two reagents for use in testing for nitric and nitrous acids. The nitrate reagent is prepared by placing 0.085 gramme of diphenylamin in a measuring flask of 500 c.c. capacity and pouring over it 190 c.c. of dilute sulphuric acid (1:3) and then adding concentrated sulphuric acid. The fluid becomes very hot, and the diphenylamin dissolves. Concentrated sulphuric acid is then added to make up to 500 c.c. The reagent keeps well. To apply the test, 100 c.c. of water are mixed with 2 c.c. of a saturated aqueous solution of sodium chloride, and 4 c.c. of the nitrate reagent are added to 1 c.c. of this mixture. The appearance of the well known blue colour indicates the presence of nitric acid. The nitrite reagent (for testing water for nitrous acid) is prepared by diluting 500 c.c. of the nitrate reagent with 200 c.c. of water. 5 c.c. of nitrite reagent are then mixed with 5 c.c. of the water to be tested. In 10 minutes the colour reaction is said to reach its greatest intensity. Both reagents can be used for the colorimetric estimation of nitrates and nitrites. The limit of sensitiveness of the nitrate reagent is given at 0.1 milligramme of  $\text{HNO}_3$  in 1000 c.c. of water, that of the nitrite reagent at 0.1 milligramme of  $\text{HNO}_2$  in 1000 c.c. of water.

### Diplosal.

The action of diplosal\*) in the treatment of angina, with special reference to acute articular rheumatism, is described

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Tillmans-Sutthoff, Zeitschrift für analytische Chemie 1911, Vol. 50, p. 473.

\*) Compare Merck's Reports 1908—1910.

in detail by O. Braun. He treated 33 cases of angina, including some of a diphtheritic nature, with large doses of diplosal. The patient was given a daily dose of 3 grammes (45 grains) in the course of 15 minutes, combined with the administration of large quantities of elder-flower tea, after which he was well covered up and allowed to perspire for two hours. As a result of this measure, the difficulty in swallowing was usually much relieved or disappeared entirely. This treatment was repeated on the following day. The author considers that the constant good result of this treatment was primarily due to the diplosal medication, as the employment of other salicylic preparations was not equally successful. The author also calls special attention to the prophylactic value of diplosal. For whereas other cases of angina were followed by severe articular rheumatism, lasting for weeks, this was absent in several cases investigated by Braun in which diplosal had been used for the treatment of angina.

R. Massalongo and U. Gasperini refer to a number of cases which show that diplosal develops a prompt anti-rheumatic and analgesic action in acute and chronic articular rheumatism, in muscular rheumatism and in neuralgia occurring in a rheumatic subject, even though diaphoresis and temperature are but little or not at all influenced. The compatibility of the preparation and the possibility it affords of introducing large amounts of salicylic acid into the system without harmful by-effects, should, in the author's opinion, in time provide a much wider range of indications for diplosal. This is confirmed in communications by L. Moschetti, who prescribed the preparation with good results in gonorrhœa. When an abortive cure is impossible, the author prefers the internal administration of diplosal in the early stages of acute gonorrhœa, as in these cases injections may lead to inflammatory symptoms. The preparation proved a most useful urinary disinfectant, which, when administered 6 times in doses of 0.5 gramme ( $7\frac{1}{2}$  grains) a day, soon cleared the urine and relieved the burning pains. Disturbances of the digestive tract were never observed. After the early

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Braun, Deutsche Medizinalzeitung 1911, No. 13.

Massalongo-Gasperini, Gazzetta medica italiana 1911, No. 23.

Moschetti, Medicina nuova 1911, No. 1.

inflammatory symptoms had subsided, the author began the local treatment simultaneously with the administration of balsams.

### **Embarin.**

An efficacious drug for the treatment of syphilis, according to H. Loeb, is a  $6\frac{2}{3}$  p.c. solution of sodium mercury-salicyl-sulphonate containing 0.5 p.c. acoine. This is a pale yellow fluid, and is placed on the market under the name of "embarin" in ampoules of 1.2 c.c. 1 c.c. of this fluid corresponds to 0.03 gramme of mercury. In order to determine the individual sensitiveness, at first 0.6 c.c. is injected. If the preparation is well borne, 1.2 c.c. are administered daily for one week, and then on alternate days for a fortnight; it is best injected into the subcutaneous tissue of the back or buttocks. Fifteen injections are usually given. This treatment acts as an energetic cure for syphilis, by means of which comparatively large amounts of mercury can be introduced into the system in a short time and without causing disturbances.

### **Enesol.**

According to the reports of E. Frey, enesol (mercury salicyl-arsenate) appears to be superior in action to salvarsan in metasyphilitic diseases of the nervous system. The author injected 2 c.c. of enesol solution (the contents of an ampoule) into the gluteal region on alternate days with aseptic precautions, and after 10 injections allowed an interval of 10 days. Altogether he usually gave 20 injections, between 15 and 30 on an average. They are said rarely to have caused pain, unless the enesol solution came into the neighbourhood of the sciatic nerve. The author never observed an inflammatory reaction at the seat of the injection, and only rarely a slight infiltration which soon disappeared. Neither during nor after the treatment did he observe gingivitis or other symptoms of poisoning. The patients bore the drug very well; only in 2 cases was there a decrease in weight, while in numerous cases the weight was increased. The metasyphi-

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Loeb, *Medizinische Klinik* 1911, p. 1853.

Frey, *Berliner klinische Wochenschrift* 1911, p. 1171. — Orvosi  
Hetilap 1911, No. 31.

lithic diseases in which enesol was used were tabes, ophthalmoplegia, cerebraesthesia, syphilitic myelitis and hemiplegia. The ptosis was cured remarkably quickly, in most cases after less than 10 injections. Frey summarizes his results as follows: Enesol is a drug having a remarkably rapid action; there is no doubt of its curative effect in paralyses of the external ocular muscles. Tabetic pains are usually cured by the drug, and the gastric and intestinal crises are apparently improved. Enesol is not only capable of inducing partial recovery of the nervous tissue, but may even effect a complete cure. A positive Wassermann result is changed to a negative one by the use of the preparation. Enesol does not give rise to general or local symptoms of poisoning and possesses an undoubted tonic action.

### Eosin-Selenium.

In recent years chemo-therapeutic tests have been carried out by various workers in order to investigate the influence of chemical substances on malignant tumours, and thus to gain information of use in the treatment of carcinoma. In the search for drugs which, without harming healthy tissues, are capable of destroying cancerous tissue, A. von Wassermann found that the salts of selenic and telluric acid were reduced on contact with cancerous tissue, with separation of selenium or tellurium, a process which was entirely selective for cancer cells, taking place in their most vital parts. Experiments with solutions of selenium and tellurium on mouse carcinoma led him to the use of eosin-selenium\*), the intravenous injection of which causes softening and absorption of the tumour. The drug itself appears to be harmless, but danger arises from another quarter, viz., the toxicity of the large masses of tumour which are absorbed give rise to untoward effects. According to von Hansemann, the selenium is precipitated in the nuclei of the carcinoma cells, thus causing their destruction. The

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A. v. Wassermann, F. Keyser, M. Wassermann, v. Hansemann, *Deutsche medizinische Wochenschrift* 1911, p. 2389.

\*) The manufacture of this preparation has not yet been sufficiently elaborated to allow the drug to be placed on the market. According to Wassermann, it forms a red powder, soluble in water. A mouse weighing 15 grammes can tolerate 1 c. c. of the 0.25 p. c. solution given intravenously.

products of disintegration then give rise to lymphoid swelling of the spleen, but no damage has been observed in other organs. It may therefore be assumed that eosin-selenium, when given in suitable doses, has no toxic action. E. Fischer and C. Klemperer have also found that compounds of vanadium and selenium have an unmistakable influence on mouse tumours. It may therefore be possible before long to discover suitable, non-poisonous compounds of selenium which can be used with benefit in the treatment of cancer in man. Eosin-selenium as yet offers no prospect of therapeutic use.

It must be emphasised that the researches of Wassermann are not as yet of any practical use; but they are of great theoretical interest in that they have shown the possibility of influencing animal tumours by means of drugs acting through the circulation, without harming the normal cells of the organism. Thus the path has been smoothed for further research; the results of Wassermann's investigations, however, are of no direct value for the treatment of carcinoma, for, as Wassermann himself remarks, mice are not people, i. e., the observations and results obtained from the study of mice do not hold good for man.

### Erepton.

The utility of rectal nutrition was much increased by the researches of Abderhalden, who was able to prove that the animal organism is capable of transforming albumin (from meat), which has been resolved to amido-acids, into albumin fit for use. A useful preparation for this purpose is now on the market under the name of "erepton". It is prepared by digesting lean meat for several weeks with pancreatic juice and succus entericus, and occurs as a brownish, hygroscopic powder, readily soluble in water; it contains about 12 p.c. of nitrogen and does not give the biuret reaction. L. Jacobsohn and B. Rewald made use of this preparation for experiments on two persons. They administered two or more enemata daily, each consisting of 250 c.c. of a

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Klemperer, Fischer, Sitzung der medizinischen Gesellschaft Berlin, 20th December 1911.

Abderhalden, Frank, Schittenhelm, Zeitschrift für physiologische Chemie 1910 Vol. 63 p. 215.

Jacobsohn-Rewald, Therapie der Gegenwart 1911, p. 119.

5 p. c. ereption solution, and found that 85 p. c. of the nitrogen of the preparation was absorbed, even if 6 enemata were given in the course of a day. When one of the patients (with cicatrised stenosis of the œsophagus) had borne the enemata well for 6 days, the authors used large continuous infusions. Of 10 to 11 grammes of ereption-nitrogen given on 3 days 46 to 53 p. c. were absorbed; on the two following days only 17 to 20 p. c. were absorbed of the 11.6 grammes given. In order to appreciate these experiments it must be remembered that in this case the rectum had been already overburdened by the numerous enemata. These experiments were intended to test the total metabolism, for which reason the authors pushed the rectal nutrition as much as possible. For the practical use of rectal nutrition, the number of enemata must either be limited to 2 or 3, each consisting of 250 to 300 c. c. of erepton solution, or else the large infusions must be given from the beginning, before the rectum is exhausted by too many nutrient enemata. For continuous infusion 1 to 2 litres of the above named solution are used. In the opinion of the authors, the nitrogen of the erepton is utilised by the organism in the same way as is the nitrogen of ordinary food. For this reason erepton appears to be superior to the other preparations of albumin and albumose for the purpose of rectal nutrition. In how far erepton can be combined with other food-stuffs must be settled by further experiments. Brandenburg successfully used a solution of 20 grammes ( $\frac{2}{3}$  oz) of erepton and 20 grammes ( $\frac{2}{3}$  oz) of maltose in 200 grammes ( $6\frac{2}{3}$  oz) of water for the rectal nutrition of patients suffering from gastric ulcers, malignant neoplasms of the œsophagus and stomach, and from inability to take nourishment on account of persistent vomiting. This solution was given rectally 3 times a day, and was borne without trouble.

### Ericolin.

In consequence of a communication by F. W. Twort, more interest has recently been aroused in ericolin, for which reason I shall refer to it here.

Brandenburg, Medizinische Klinik 1911, p. 16.

Twort, Zentralblatt für Bakteriologie, I. Abteilung Referate, 1909, Vol. 44, p. 65.

Ericolin is a glucoside\*) contained in the leaves of *Ledum palustre* L., *Calluna vulgaris* Salisb. (*Erica vulgaris* L.) and other *Ericaceæ*; so far it has not been used in therapeutics. Nor have exhaustive pharmacological tests been made, although heather was formerly a popular remedy for the cure of stone and bladder troubles, and for weak eyes. Only Kanger used it for a few experiments on frogs, which showed that only very large doses have a toxic action, for 0.1 gramme injected into the dorsal lymph-sac of an animal weighing 40 grammes caused no symptoms within 24 hours. In another frog 0.2 gramme caused death in 6 hours. Ericolin has, however, a poisonous action on microbes, as has been shown by Twort. He states that the glucoside kills most kinds of micro-organisms, especially the bacilli of the coli group and various cocci, but that it has only a slight influence on acid-fast bacilli. Twort therefore suggested that tubercle bacilli might be cultivated directly, with the help of ericolin, from sputum contaminated by other micro-organisms, and that by this means pure cultures of human tubercle bacilli might be obtained. For this purpose he used a 2 p.c. aqueous solution of ericolin, with which he treated the sputum for three-quarters to one hour at 38° C. in the incubator. If the cultures are now transferred to the Dorset egg-nutrient medium, according to the author, a pure culture of tubercle bacilli is obtained in 14 to 28 hours.

The preparation and the properties of ericolin were first described by Rochleder, and were supplemented by Schwarz, Kawalier and Thal. Thal, who like Rochleder prepared the drug from *Ledum palustre* L., describes it as a brownish-yellow, hygroscopic, amorphous body, without smell, which decomposes already under 100° C. The chemical formula —  $C_{26}H_{30}O_3$  — proposed by him is without value in view of the questionable purity in which the glucoside

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\*) Compare J. Orley, *American Journal of Pharmacy* 1872, Vol. 2, p. 250.

Kanger, *Archiv für experimentelle Pathologie* 1903, Vol. 50, p. 61.  
— *Chemiker-Zeitung* 1903, p. 794.

Rochleder, *Sitzungsberichte der k. k. Akademie der Wissenschaften in Wien* 1852, p. 307.

Schwarz, *ibid.* 1853, p. 298.

Kawalier, *ibid.* 1853, p. 290.

Thal, *Dissertation Dorpat* 1883. — *Pharmazeutische Zeitschrift für Russland* 1883, p. 209, 233, 249, 265, 281.

was obtained by the author. Kanger was right in doubting that the ericolins described in the literature were uniform chemical bodies. He believes that different resinous and glucosidal bodies are present in *Ledum palustre* and in the *Ericaceæ*, which probably represented the ericolin of these authors. Nor have I been more successful in preparing a pure, uniform ericolin. But in order to meet the many demands, I supply, when specially ordered under the name of "ericolin", a preparation consisting of a purified extract which is very rich in ericolin. It was with this preparation that Prof. Twort carried out his experiments.

Since the substance in question is not a pure uniform body, as explained above, I have not included ericolin in my list.

### Erythrol Tetranitrate.

This preparation\*), according to N. Ortner, who has had many years' experience in the use of this drug, is deserving of more consideration in the treatment of arterio-sclerotic affections. It is capable in some cases of suppressing an existing attack of stenocardia, and is also often useful as a prophylactic against the recurrence of attacks of angina. The author, however, deprecates the use of large doses such as were suggested by Bradbury and Oliver (4 c.c. of an alcoholic solution of 1:60, i. e., about 0.07 gramme of erythrol tetranitrate), as they may give rise to headache, vertigo and congestion of the head. He prescribes the preparation with good results as follows:

Rp. Erythrol tetranitrate 0.1—0.2 gramme ( $1\frac{1}{2}$ —3 grains).

Ext. et pulv. glycyrrhiz. q. s. ut ft. pil. No. 20.

2 of the stronger pills are given daily during the attack, while 3 of the weaker ones are administered daily between the attacks. The weaker pills are given for a considerable time, and, according to the individual case, the daily dose may be reduced by 1 to 2 pills.

### Ether.

L. Burkhardt again reports on intravenous ether anaesthesia\*\*), and describes his experience in over 250 cases. He

\*) Compare Merck's Report 1896.

Ortner, Jahreskurse für ärztliche Fortbildung 1911, No. 2, p. 46.

Bradbury, British Medical Journal 1895, II, p. 1213.

Oliver, British Medical Journal 1896, I, p. 1375.

Burkhardt, Münchener medizinische Wochenschrift 1911, p. 773.

\*\*) Compare Merck's Report 1910.

points out especially that so far no damage has ever been done to the blood by his method. He also asserts that by the use of ether alone no renal disturbances occurred, so long as the organs were healthy. The 5 p.c. solution of ether in normal saline, as prescribed for infusion, when used at a temperature of 28° C. (82.4° F.) causes no cooling of the patients, as was feared might be the case; at any rate the cooling is no greater than that which occurs after inhalation anæsthesia. As regards the effect of intravenous ether anæsthesia on the blood pressure, a rise of any importance only occurs if it is pathologically raised, or perhaps, as in severe arterio-sclerosis, if it is pathologically lowered. In the latter case, so long as the lowering of the blood pressure is not due to organic disease of the heart muscle, the infusion anæsthesia will act favourably, and is indeed directly indicated. Care is necessary, however, if severe arterio-sclerosis with abnormally high blood pressure is present. In order to attain a sufficient concentration of ether in the arterial blood for deep anæsthesia, about 80 c.c. of the 5 p.c. solution of ether per minute are necessary. If by the use of ether alone and with correct technique the anæsthesia is not sufficiently deep and is not free from reflexes, we are, according to Burkhardt, dealing with individuals who are incapable of being deeply anæsthetised by ether. The author also refers to the severe reproach of the possible danger arising from embolism and thrombosis. In his experience, with correct technique, the formation of clots at the point of infusion can certainly be avoided. Thrombi which form at the close of the anæsthesia at the point where the vein has been tied, as is always the case when a vein is ligatured, he says are not dangerous. Whoever is afraid of them must avoid the use of any form of intravenous injection.

Intravenous ether anæsthesia appears to have special advantages when combined with isopral. Burkhardt prescribes the separate infusion of the two drugs. First, without previous injection of scopolamine-morphine, a filtered, sterile, 1.5 p.c. solution of isopral (in Ringer's solution) is instilled drop by drop in rapid succession (40 c.c. per minute), until the stage of tolerance is reached; then the tube is clamped and the one leading to the ether solution is opened. The ether is now infused quite slowly and the rate of flow is only

temporarily increased when the reflexes return. The author states that more than 200 c.c. of isopral solution should never be used. His method is contra-indicated in myodegeneration cordis, severe arterio-sclerosis, nephritis, severe icterus, cholæmia, congestion and general plethora; it is specially indicated in conditions of collapse, loss of blood, cachexia and conditions of exhaustion, disturbances of the respiratory organs and peritonitis, also in operations on the head and neck, and in children in staphyloorrhaphy.

K ü m m e l l considers intravenous ether anæsthesia specially suitable for operations in weakly individuals and in carcinoma, for the reason that only a small amount of ether is used and this is quickly eliminated by the lungs. By means of the use of 250 c.c. of the 5 p.c. solution of ether in normal saline, on a average, the patient is anæsthetised in 10 minutes, and there is no fear that the customary by-effects of anæsthesia, as for example vomiting, will supervene. Thrombosis may be avoided by following up the transfusion with an injection of normal saline solution. R. H a g e m a n n, in testing Burkhardt's procedure, observed nothing pointing to the probability of thrombosis; three cases of post-mortem examination showed a complete absence of thrombosis. The author was altogether well satisfied with the results of intravenous ether anæsthesia, but he lays great stress on the method of preparation of the ether solution, certainly a matter of considerable importance. At the temperature recommended by Burkhardt, he observed that during the infusion a layer of ether separates on the surface of the solution of ether and normal saline, which evaporates very slowly. In his opinion it is therefore possible that when a fresh supply of solution is added a mixture is formed containing more than 5 p.c. of ether, which might lead to hæmoglobinuria. He therefore employs the solution of ether and normal saline at a temperature of 38° C. (100·4° F.), at which temperature only 4·68 p.c. of ether is said to dissolve, but this amount is fully sufficient. If at this temperature any ether should separate, it evaporates very rapidly. The mixture must be prepared at the ordinary temperature, and can then be warmed to

Kümmell, *Therapie der Gegenwart* 1911, p. 272. — *Verhandlungen auf der Versammlung norddeutscher Chirurgen in Hamburg, January 1911.*

Hagemann, *Münchener medizinische Wochenschrift* 1911, p. 1497.

38° C. by placing in warm water. It is inadvisable to add the ether to the normal saline solution warmed to 38° C., as ether boils at a low temperature. Care should be taken in this procedure, because too great an evaporation of ether should be avoided under all circumstances.

Udewald points out in his thesis, for which he has collected the experiences gained in the Bethany Hospital in Hörde i. W., that the by-effects of intravenous ether anæsthesia, which are feared by some, can be avoided. For operations on the head and neck intravenous ether anæsthesia is, in his opinion, the "method of choice". He believes it to be an advance in the technique of anæsthesia and to give excellent results in suitable cases. He gives as special indications for its use: pathologically lowered blood pressure, compensated cardiac lesions and nervous cardiac disturbances; for cachectic and anæmic individuals and for probable considerable hæmorrhage. It should be used with caution in cases of difficult respiration and in severe icterus, and should be entirely avoided in diseases of the blood vessels accompanied by raised blood pressure, diseases of the cardiac muscle, renal disease, cholæmia, congestion and general plethora.

From a communication by S. Tsakoma regarding intravenous ether anæsthesia it appears that the kidneys may be damaged by too rapid infusion of the ether solution. With the method itself the author was well satisfied.

Burkhardt's method induced C. Arnd to try the solution of ether in saline rectally, and its harmlessness when given this way was soon established. One and a half hours before the operation the author administered an injection of 0.02—0.04 gramme ( $\frac{1}{2}$ — $\frac{2}{3}$  grain) of omnopon (pantopon), half an hour before the operation an injection of scopolamine-omnopon, and immediately before the operation one litre of the ether solution was given rectally. In most patients this method of treatment is said to cause immediate unconsciousness. As necessity arises a further amount of ether solution should be allowed to flow in at suitable intervals; this can

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Udewald, Dissertation Bonn 1911.

Tsakoma, Gynäkologische Rundschau 1911, No. 3.

Arnd, Verhandlungen der Versammlung der deutschen Gesellschaft für Chirurgie zu Berlin, April 1911. — Allgemeine medizinische Zentralzeitung 1911, p. 305.

be done from an infusion-spray bottle. By employing mixtures of ether and oil for similar purposes Rehn obtained unsatisfactory results.

The experiments on dogs, carried out by T. S. Githens and S. J. Meltzer, are not without interest in the treatment of strychnine poisoning; they showed that even a double lethal dose of strychnine given by intratracheal insufflation under ether anæsthesia did not cause the death of a single animal. When chloroform was used, these favourable results were not obtained.

### Ethyl Bromide.

As a result of much experience in the use of ethyl bromide in dentistry, Breitbach declares this anæsthetic to be free from danger when carefully employed, and to be effective for all dental operations. K. Cohn would prefer to avoid the practice of dealing with the stage of excitement in alcoholic patients by binding the patient to the operating chair and would instead administer suitable drugs. He therefore recommends giving a dose of 0.6 gramme (10 grains) of bromural or an injection of scopolamine-morphine before the operation. In order to avoid the possibility of delayed intoxication after ethyl bromide anæsthesia F. Mounier points out that two factors should be taken specially into consideration, namely the age of the patient and the presence of digestive disturbances. Although he recognises the convenience of ethyl bromide anæsthesia, he considers it of importance, in the treatment of children, to examine carefully the digestive organs before the performance of laryngological, otological and rhinological operations; for if acute enteritis be present, symptoms of delayed intoxication might ensue. Should this examination lead to the discovery of gastro-intestinal disturbance, operative measures should be postponed until this condition has subsided. Post-operative contingencies, which manifest themselves as catarrhal conditions are, in the author's opinion, no reason for avoiding the use of this valuable anæsthetic. Should by-effects of this nature occur, they can

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Rehn, *ibid.*

Githens-Meltzer, *Berliner klinische Wochenschrift* 1911, p. 669.  
Breitbach, *Deutsche medizinische Wochenschrift* 1911, p. 374.

Mounier, *Archives internationales de laryngologie* 1911, January  
— *Münchener medizinische Wochenschrift* 1911, p. 1150.

readily be removed by washing out the bowel, and administering a fluid diet.

### Ethyl Chloride.

A paper by M. Behr, in which the author describes the use of ethyl chloride and its advantages in the performance of short operations, is of particular interest to practitioners. As special advantages he points out the relative harmlessness of the drug when used in suitable doses, its pleasant odour which facilitates its employment, more especially for children, also the absence of a feeling of suffocation and the diminution of the stage of excitement, the rapid induction of anæsthesia, the speedy return to consciousness, and finally the total absence of after-effects. Behr, like Herrenknecht, considers the employment of a suitable mask of importance. Over a wire frame, similar to Esmarch's mask, the basal ring of which is copied from the curve of Roth-Dräger's mask, a self-retaining hoop is tilted, which is fastened at two points and can be easily removed. Around this hoop the author, by means of a piece of thread (as in Esmarch's mask), draws a piece of waterproof material, in which an opening is left for the patient's mouth. This opening is covered from within by a piece of absorbent gauze, and the whole is tilted over the wire frame like a roof. The mask is now ready for use. On account of the intense action of ethyl chloride, sudden anæsthesia should be avoided. This mask also enables a sufficient dose to be given in a simple manner. About 1 c. c. (17 min.) from the metal-stoppered bottle is sprinkled on the gauze from within, the mask is then applied and more ethyl chloride administered through the opening in the waterproof material. At short intervals the opening is closed by applying a finger, until the amount which has been sprinkled on is used up. It is well not to hold the bottle of ethyl chloride too far away, as a surplus of ethyl chloride tends to prevent the formation of ice on the mask. The preparation for the anæsthesia is carried out in the same way as for ether or chloroform. In lengthy anæsthesia Behr has frequently begun with ethyl chloride and continued with chloroform, which method is said to effect a saving

of chloroform. The author also points out that a second short period of anæsthesia in the same patient by means of ethyl chloride, and following immediately upon the first, takes effect more quickly. Children take it well in this manner. It is thus easy, after tonsillectomy for instance, to wait until the bleeding has ceased, and after a few breaths of ethyl chloride to remove the adenoids, or during the removal of several teeth to allow the patient to rinse his mouth between the separate extractions.

H. Schwerin considers that ethyl chloride anæsthesia, on account of its great usefulness, deserves more consideration than has in his opinion been accorded to it by practitioners. He fears, however, that the recommendation of special masks and preparations may prevent many practitioners from using such a valuable drug as ethyl chloride. He believes, as the result of his experience, that an ordinary chloroform mask acts perfectly well for the administration of ethyl chloride for small operations to be performed in the consulting room. He gives several practical hints, which can be recommended for perusal in the original paper by those interested.

D. Kulenkampff reports on the employment of the stadium analgeticum of ethyl chloride anæsthesia. This should, in his opinion, be more used, especially in cases unsuited for prolonged ether anæsthesia, such as short operations, small incisions, painful bandaging, etc. In these cases ethyl chloride is said to be superior to ether in rapidity of action and absence of irritant effects. By the use of 30 to 60 drops of ethyl chloride, and for strong patients of 80 to 100 drops, the analgesic state is reached in about one-third to three-quarters of a minute.

### Ethylene Diamine Hydrate.

Ethylene diamine hydrate,  $\text{NH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2 \cdot \text{H}_2\text{O}$ , is a colourless, or pale yellow fluid with a specific gravity of 0.965 to 0.970, miscible with water in all proportions.

J. A. Siemssen used a 10 p.c. solution of the preparation as a test for uranium salts, after he had discovered

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Schwerin, *Berliner klinische Wochenschrift* 1911, p. 302.

Kulenkampff, *Beiträge zur klinischen Chirurgie* 1911, Vol. 73, No. 2.

Deutsche medizinische Wochenschrift 1911, p. 2136.

Siemssen, *Chemiker-Zeitung* 1911, p. 139 and 742.

that with uranium solutions a light yellow, crystalline precipitate is formed. This reaction is said to take place in very dilute uranium solutions, and to be as delicate as Aloy's test\*) for uranium. For the quantitative estimation of uranium salts the ethylene diamine solution is added drop by drop to a solution of these salts until no further precipitate is formed. The uranium compound, which is insoluble in water, quickly settles, is then collected on a filter, washed with cold water and, together with the filter, incinerated in a platinum crucible. The residue is heated to redness until constant weight, and, after cooling in an exsiccator, it is weighed as  $U_3O_8$  (uranium uranate). It is not practical to dilute the ethylene diamine more than suggested above, for a gelatinous precipitate is obtained which filters with difficulty. Other metallic salts also give precipitates with this reagent. The author has not yet published his report on this point.

### Ethyl Hydrocupreine.

Through the chemo-therapeutic researches of J. Morgenroth and R. Levy interest in the derivatives of quinine has been awakened, and more especially in ethyl hydrocupreine. Its chemical relationship to quinine may be briefly indicated in the following formulas:

Cupreine	$C_{19}H_{20}N_2 \cdot OH \cdot OH$
Quinine	$C_{19}H_{20}N_2 \cdot OH \cdot OCH_3$
Hydrocupreine	$C_{19}H_{22}N_2 \cdot OH \cdot OH$
Methyl hydrocupreine (Hydro- quinine)	$C_{19}H_{22}N_2 \cdot OH \cdot OCH_3$
Ethyl hydrocupreine	$C_{19}H_{22}N_2 \cdot OH \cdot OC_2H_5$
Quinethylin (according to Grimaux and Arnaud)	$C_{19}H_{22}N_2 \cdot OH \cdot OC_2H_5$

As regards the more exact knowledge of these substances the works of Paul, Cownley, Oudemans and Hesse, and "Arzneimittelsynthese" of S. Fränkel may be consulted.

Morgenroth experimented with ethyl hydrocupreine on mice infected with pneumococci, in order to test the prophylactic and curative action of the drug. For subcutaneous injec-

\*) Compare Merck's Reagenzien-Verzeichnis 1908, p. 4.  
Morgenroth-Levy, Berliner klinische Wochenschrift 1911, No. 34,  
p. 1560 and No. 44, p. 1979.

tion a 0.75 p.c. aqueous solution of the sulphate or hydrochloride was employed, of which 0.5 c.c. was administered to a mouse for a dose for every 20 grammes of weight. These experiments led to the discovery that ethyl hydrocupreine is far superior to methyl hydrocupreine (hydroquinine) as regards action in pneumococcal infection. The protective action of quinine against this infection is so slight and so rarely obtained that, according to the author, it would easily have escaped the observation of the investigator had he been satisfied with the results of a small number of experiments. Morgenroth's discovery is of importance for the fact that by the use of small, harmless doses a prophylactic action can be obtained. But the curative action of ethyl hydrocupreine also seems hopeful, to judge by the author's results, although not too much should be expected from it as yet. For half the animals used in the experiments were cured, although they were the subjects of a fully developed fatal infection.

### Eucerin.

The facility with which eucerin\*) is absorbed by the human and animal skin makes this preparation specially suitable as a basis for ointments, e. g., for potassium iodide ointment. According to R. Schlenker, a 10 p.c. potassium iodide eucerin ointment is readily absorbed through the intact skin of man, dogs, sheep etc., so that in man iodine appears in the urine, on an average, in 3 hours, and in domestic animals in 2 hours. In man the excretion of iodine after the application of 10 grammes ( $\frac{1}{3}$  oz) of a 10 p.c. potassium iodide eucerin ointment continues for as long as 36 hours, in dogs for 5 to 6 hours, and in sheep for 4 to 5 hours. A dose of 2.5 grammes (40 grains) of the ointment named is just sufficient to give a positive iodine reaction in the urine. The author considers the buttocks to be the most suitable region for the application of the iodine ointment.

Unna recommends as a substitute for the ordinary glycerin ointment a mixture of 20 grammes ( $\frac{2}{3}$  oz) of anhydrous eucerin and 80 grammes ( $\frac{2}{3}$  oz) of glycerin. The advantages of this mixture are at once evident when it is

\*) Compare Merck's Report 1907.

Schlenker, Dissertation Giessen 1911.

Unna, Medizinische Klinik 1911, p. 95.

considered that its high percentage of glycerin renders it exceedingly hygroscopic and that the eucerin it contains gives it the properties of a fatty ointment. According to Unna, the mixture rightly deserves the name of "glycerin ointment", rather than the other mixtures to which this name is applied.

### Eudermol.

A. Kölliker mentions a communication by Fettick with regard to this remedy for scabies\*). The good results obtained in scabies encouraged the author to try the effects of the preparation (nicotine salicylate) in the treatment of other skin diseases in veterinary practice. The results are said to have been very satisfactory in non-parasitic eczema, favus, herpes, and in scabies due to sarcoptes and acarus. The author speaks highly of the drug, especially on account of the rapidity with which it softens and loosens the scabs and allays irritation, while it exerts a durable influence on the acute inflammatory symptoms; in addition, it is colourless and odourless, properties which render the preparation suitable for application to house dogs. Applied to hounds it does not interfere with the sense of smell, as creolin has been observed to do. It has also been found useful for sheep scab, and is said to bring about a rapid and complete cure.

### Eulatin.

This remedy for whooping cough\*\*), according to the reports of R. Weissmann and A. Soucek, is useful as a symptomatic. In Weissmann's experience its action is more rapid and striking the earlier it is used. The attacks of coughing soon diminish, become less severe and shorter, and their spasmodic character, to which the frequent occurrence of vomiting is chiefly due, gives place to a looser cough. To children 1 tablet (0.25 gramme [4 grains] of eulatin) is given in warm liquid or porridge every 2 to 4 hours, according to the severity and number of the attacks. Or the

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\*) Compare Merck's Report 1898.

Kölliker, Deutsche tierärztliche Wochenschrift 1911, p. 167.

Fettick, Zeitschrift für Tiermedizin 1911, Vol. 5.

\*\*) Compare Merck's Report 1908.

Weißmann, Allgemeine medizinische Zentralzeitung 1911, p. 227.

Soucek, Österreichische Ärzte-Zeitung 1911, p. 219.

drug may be given in the form of powder, or as a mixture, according to the following prescription:

Rp. Eulatin.	3.0 grammes (45 grains)
Aq. laurocer.	2.5 grammes (40 min.)
Syrup.	10.0 grammes ( $\frac{1}{3}$ oz)
Aq. ad	100.0 grammes ( $3\frac{1}{3}$ oz)

(A small teaspoonful every 2 hours.)

Soucek prescribed eulatin for children of 3 months and observed no bad effects, even after daily doses of 1 gramme (15 grains) (4 tablets). He gave 3 tablets a day to children under one year, 4 to 5 tablets for those over one year; later, to increase the action, 4 tablets to children under one year, and 6 tablets to those over one year, and 8 tablets to children over 4 years, and he believes that the dosage may be still further increased without harm. As eulatin also acts slightly as an expectorant and a sedative, the author tried it in bronchitis, and by its means, without employing the usual drugs, he effected the cure of 10 ordinary cases of bronchitis and 2 cases of bronchitis following measles. He naturally supplemented the treatment by suitable hygienic measures.

### Ferric Chloride.

A solution of ferric chloride containing hydrogen peroxide was suggested by J. Mindes as a test for a number of substances. It is prepared by mixing 1 part of a 10 p. c. aqueous solution of ferric chloride with 1 part of alcohol and 3 parts of solution of hydrogen peroxide (12 p. c.). Of the numerous tests described by the author, only a few will be cited.

Adrenalin. 10 drops of adrenalin added to 10 c. c. of water and 10 drops of the reagent give a grass-green coloration, which changes to red in about a minute. Morphine. A trace of morphine is coloured light green by one drop of the reagent. 0.01 gramme of morphine dissolved in 10 c. c. of water remains clear on the addition of one drop of the reagent; the further addition of morphine to the mixture up to 0.1 gramme gives a pale blue coloration, which disappears on shaking. Only when 0.25 gramme of morphine and 5 drops of the reagent are present does a permanent blue coloration result. On heating, the colour of this mixture also disappears.

Mindes, Pharmazeutische Post 1911, p. 687.

Quinine. 0.25 gramme of quinine hydrochloride dissolved in 10 c.c. of water gives with 5 drops of the reagent an orange-yellow coloration, which changes to brown on heating, and assumes a greenish colour on the addition of a few drops of fuming nitric acid. Podophyllin. A solution of 0.01 gramme of podophyllin in 2 c.c. of alcohol is coloured olive-green by one drop of the reagent.

### **Ferrosajodin.**

Ferrosajodin has been favourably criticised by Echtermeyer who tried it chiefly for scrophulous lymphadenitis in children. Of the 50 cases treated, the preparation proved successful in 46; in 2 cases it had to be stopped on account of slight gastric disturbances, and in 2 cases the appearance of caseous softening of the glands necessitated their removal. The administration of 2 tablets daily of the drug was well borne. Most of the children came for treatment on account of nasal catarrh, sore throat, adenoid growths, enlarged tonsils and discharge from the ear, and these affections were dealt with before commencing the sajodin medication. But cases also occurred in which the cause of the trouble was not due to the above conditions. The author has observed a favourable influence on enlarged glands by the use of other drugs, but he considers the sajodin tablets to be specially suitable for administration to children on account of their pleasant taste, resembling chocolate. M. Radziejewski arrived at the same conclusion in the treatment of scrophulous eye affections. According to him, sajodin is a useful adjunct to local treatment, as it improves the general condition, the appetite and the psychic state of the children, and thus adds considerably to the improvement of the patient. In order to prevent recurrences, it is well to continue the administration of sajodin for a time after the local treatment of the eyes has been stopped. The author usually prescribed it in doses of 0.5 gramme ( $7\frac{1}{2}$  grains) in such a way that children of 2 to 4 years were given 2 tablets (of 0.5 gramme [ $7\frac{1}{2}$  grains]) a day, and an extra tablet for each year of their age, up to 6 tablets. For younger children it is better to give the sajodin in the form of an emulsion.

Echtermeyer, *Medizinische Reform* 1911, No. 6.

Radziejewski, *Medizinische Reform* 1911, Vol. 19.

**Fibrolysin.**

Among the newer drugs, fibrolysin certainly stands today in the foreground of therapeutic interest. Nor is this surprising when its now established action in softening scar tissue is taken into consideration. For the removal of scar tissue, whether due to operative procedure or to pathological processes, comes into the province of both the clinician and of the general practitioner. A. Thost, in his interesting book on the contractions of the upper air-passages after tracheotomy and their treatment, states that fibrolysin is very well borne by children. In his experience it gives rise to no secondary effects, while it has a distinct action on the scar tissue, which became softer and more pliant, so that dilatation could be carried out more rapidly. The observations made by the author on a boy of 11, who had previously undergone tracheotomy, and which confirmed the brilliant effects of fibrolysin, lead him to suggest that an injection of fibrolysin be made at least 12 hours before the introduction of a dilator, if dilatation is to be performed without a cannula. But even in cases in which a cannula had already been introduced and in which the author used his so-called wedge method, he was convinced of the favourable effect of fibrolysin on scar tissue. He was able to demonstrate by means of a mirror that the preparation, soon after its injection, gives rise to considerable hyperæmia and congestion, and that the softening lasts about 24 hours.

Further communications as to the effect of fibrolysin injections in softening scar tissue have been made by Langes, Huitfeld, Sidorenko, Suñer, Wockenfass, and von Bernd. Langes describes a case in which after an operation for gall-stones, the formation of internal adhesions gave rise to jaundice with severe pain. A series of 12 in-

Thost, Wiesbaden 1911. Published by J. F. Bergmann.

Langes, *Therapeutische Monatshefte* 1911, No. 2, p. 104.

Huitfeld, *Norsk Magazin for Lægevidenskaben* 1911, No. 1.

Sidorenko, *Deutsche Zeitschrift für Chirurgie* 1911, Vol. 110, No. 1—3.

Suñer, *Clinica Castellana* 1910, 15<sup>th</sup> July. — *Medicina de los niños* 1911, p. 236.

Wockenfass, *Deutsche medizinische Wochenschrift* 1911, No. 36, p. 1560.

Bernd, *Direktionsbericht des k. k. Wohltätigkeitshauses Baden bei Wien* 1910, p. 21.

jections of fibrolysin brought about the total disappearance of the attacks of colic and of the pre-menstrual troubles which had been present. Thus fibrolysin treatment proved successful, and yielded a permanent result. Huitfeld also emphasises the value of the preparation in bringing about the pliability of scars and adhesions and of causing the disappearance of the pain connected with them. von Bernd states that the success of fibrolysin treatment is undeniable. It is apparent in the gradual, complete return of the function of the joints which had been ankylosed. The results of fibrolysin treatment were especially brilliant in patients who had been prepared by a course of baths. It is difficult to understand why Sidorenko seeks to deny the influence of the preparation on scar tissue. Wockenfuss treated a young man, whose face was much disfigured by scars due to acne necrotica from which he had recovered years ago, with injections of fibrolysin, which were applied as near to the scars as possible twice a week. The patient was given altogether 20 injections. The cosmetic effect was most satisfactory and encouraged a repetition of the injections, resulting in the disappearance of the disfiguring scars. In consideration of the extremely disfiguring effect of the scarring and of the previous unsuccessful treatment by means of countless internal and external remedies, the result was such as to cause the author to advise the use of fibrolysin in similar cases.

The value of fibrolysin in strictures is reported upon by J. Kowats, F. Ploch and A. Nathan. Kowats gave 4 injections for cicatricial stenosis of the pylorus, which led to rapid improvement of the stenosis and of the general health. Ploch had a similar result in a case of œsophageal stricture, which he treated by means of fibrolysin and bougies, without requiring the patient to rest, and which was eventually cured. A point in the technique noted by the author is that the injections, whenever possible, should be made into a thick bundle of muscle in order to obviate pain and reaction. He considers the gluteal muscles and the deltoids the most suitable; apart from the garlic-like taste and smell, he has never observed troublesome symptoms to result from the employment

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Kowats, Budapesti Orvosi Ujsag 1910, Therapeutische Monatshefte 1910, p. 721.

Ploch, Deutsche medizinische Wochenschrift 1911, p. 358.

Nathan, Zeitschrift für Urologie 1911, Vol. 5, No. 2.

of fibrolysin. Nathan found that 10 to 15 injections were usually sufficient in the treatment of urethral strictures. He gave 3 injections a week, as well as special treatment. He agrees with other observers in considering fibrolysin an excellent auxiliary to dilatation in the treatment of strictures.

Interesting experiments were carried out by von Kuester with the use of fibrolysin in carcinoma of the œsophagus and of the cardia. His idea was, by means of injections of fibrolysin, to transform the hard variety of cancer into a softer form, or at least to diminish or prevent the formation of scars and callosities in the hard form. In this way, by means of the regular passage of bougies, he aimed at keeping an open way for the passage of food and thus to reduce the necessity for gastrostomy with its unsatisfactory results. In suitable cases he injected the contents of one ampoule of fibrolysin subcutaneously into the epigastrium twice a week, and passed bougies an equal number of times. By means of this treatment life became more bearable for the patients and some even felt permanently well.

F. Ehrlich believes that the tenderness to pressure or the painfulness of small umbilical and epigastric hernias is due to the more or less extensive adhesions between the hernial ring and the surrounding tissue. As a diminution of tension may be brought about by the application of adhesive plaster, in the author's opinion the same result should be produced by the loosening and softening of the adhesions. The experiments of Ehrlich have confirmed the truth of this supposition. It was found that injections of fibrolysin are effective in the treatment of this form of hernia. For this purpose the contents of one ampoule are injected daily or every 2 to 3 days deep into the abdominal muscles, the injected fluid being distributed by massage.

In tendovaginitis crepitans injections of fibrolysin give promise of being a useful method of treatment, as is shown in a communication by E. G. Oser. Twenty cases were, without a single exception, cured by the author in 3 to 4 days by means of a single injection, even those cases in which other means, such as the use of iodine and rest for

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Kuester, Medizinische Klinik 1911, No. 25.

Ehrlich, Archiv für Verdauungskrankheiten 1911, Vol. 17, No. 1.

Oser, Wiener klinische Wochenschrift 1911, No. 44.

the sympathetically affected groups of muscles, had completely failed. But even in those cases in which iodine treatment is successful, the process of healing is much more prolonged than when fibrolysin is used.

F. Mendel reviews the use of fibrolysin, its action and its secondary effects. Apart from the specific action of the drug upon scar tissue, it only rarely exhibits troublesome secondary symptoms. Mendel considers the so-called fibrolysin intoxications, which are manifested by headache, vomiting, rise in temperature, and which are observed from time to time to occur after several applications of the preparation have been borne without reaction, to be due to anaphylaxis. As is well known, Starkenstein has shown that fibrolysin promotes the hydrolysis of collagen. In this way the employment of fibrolysin causes albuminoid substances to appear in the blood; these give rise to the formation of antibodies, which react with the albumin bodies appearing on the further employment of fibrolysin. The fact that these reactions are directly connected with the curative effect of fibrolysin is manifest, for in these cases the therapeutic effect of the drug is usually most striking.

For the alleviation of the supposed symptoms of intoxication Mendel recommends the following prescription:

Rp. Codein. phosph.                      0.05 gramme ( $\frac{3}{4}$  grain)  
Phenacetin.  
Aspirin.                                      aa 0.5 gramme ( $7\frac{1}{2}$  grains)  
M. Ft. pulv. Mitte VI.

Sig.: 1 powder to be taken every 3 hours.

In an instructive case of arthritis deformans, the author shows that a speedy effect can be produced by the use of fibrolysin suppositories, as well as by means of injections. In connection with the communications of Mendel, attention may be drawn to two cases observed by K. Friedmann and M. Szanto, in which the injection of fibrolysin caused in one case purpura hæmorrhagica and in the other case vertigo and vomiting.

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Mendel, Therapie der Gegenwart 1911, p. 155.

Friedmann, Therapie der Gegenwart 1911, p. 205.

Szanto, Gyogyaszat 1911, No. 32.

According to Stöltzner, fibrolysin is specially useful in chronic inflammation of the lungs. In the case of a 7-year-old boy, suffering from an irregular febrile condition, numbness and bronchial breathing, and in whom contraction of one side of the chest and curvature of the spine had already taken place, the author administered 10 injections of fibrolysin in the course of 3 weeks, with the result that the fever disappeared and the weight was considerably increased. Stöltzner therefore recommends that similar cases should be treated with fibrolysin.

Externally fibrolysin has been prescribed with good results by J. Zilz for *lingua villosa nigra disseminata*. His treatment consisted in swabbing the black patches with a warm, 15 p.c. aqueous solution of fibrolysin. The application was repeated twice daily. On the third day scarcely a trace of the black patches could be seen. For the after treatment the tongue was sprayed with a 5 p.c. solution of perhydrol.

In veterinary medicine fibrolysin has also proved of use in many ways, as I have on various occasions pointed out in these Reports. Recently Dun, J. Breedveld, Sepp, Wilhelmi, Barnick, Spaeth, Hengst, Bergschicker, M. Jöhnk, Russanoff, C. Hochenadl and A. Révész have published their results with fibrolysin. The cases described deal with *morbus maculosus*, cicatrices following wounds of the fetlock, thickened tendons, contracted tendons following upon tearing of the tendons, teno-synovitis, phlegmon with lameness, elephantiasis glabra and similar processes in horses, and generalised sarcomata of swine. The

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Stöltzner, *British Medical Journal* 1911, II, p. 486.

Zilz, *Archiv für Zahnheilkunde* 1911, No. 8.

Dun, *Münchener tierärztliche Wochenschrift* 1911, No. 35.

Breedveld, *Österreichische Wochenschrift für Tierheilkunde* 1911, No. 39.

Sepp, *Münchener tierärztliche Wochenschrift* 1911, No. 2.

Wilhelmi, *Schweizer Archiv für Tierheilkunde* 1911, No. 2.

Barnick, *Berliner tierärztliche Wochenschrift* 1911, No. 3.

Spaeth, *Berliner tierärztliche Wochenschrift* 1911, No. 9.

Hengst, *Berliner tierärztliche Wochenschrift* 1911, No. 20.

Bergschicker, *Berliner tierärztliche Wochenschrift* 1911, No. 21.

Sustmann, *Berliner tierärztliche Wochenschrift* 1911, No. 34.

Jöhnk, *Münchener tierärztliche Wochenschrift* 1911, No. 6.

Rusanoff, *Veterinarnij Wratsch* 1911, No. 39.

Hochenadl, *Münchener tierärztliche Wochenschrift* 1911, No. 11.

drug was applied subcutaneously, intramuscularly or intravenously in average doses of 10 c.c. In most cases a partial or complete cure was effected, but cases occurred in which the treatment failed. Hengst also treated a dog, suffering from urethral stricture, with marked benefit, but without obtaining a complete cure. Dun therefore came to the conclusion that fibrolysin was only capable of curing that form of thickened tendon which was preceded by traumatic tendovaginitis or tendinitis and which persisted after the disappearance of all acute symptoms. In long-standing processes, on the other hand, he has little faith in the action of fibrolysin.

### Gelatin, Sterilised

In melaena neonatorum F. de Bra and F. Nohl have obtained excellent results by the use of gelatin injections. According to de Bra, it is absolutely essential that the injections should be administered under the strictest aseptic precautions, that a good and absolutely sterile preparation, such as *gelatina sterilisata Merck*, should be employed, that this be injected in amounts of 10 up to at most 20 c.c. and that the injections should be given as early as possible, but never at the cost of faulty asepsis, or by using an unreliable preparation of gelatin. If these two conditions cannot be completely complied with, it is better to wait until this is possible. Nohl considers gelatin injections to be the most effective means of treating melaena neonatorum vera, and also recommends its use for omphalorrhagia idiopathica.

A further indication for gelatin injection is, according to Finkelstein, given by pachymeningitis hæmorrhagica interna in children. In order to prevent the recurrence of hæmorrhage in these cases, the author gave repeated injections of *gelatina sterilisata*, viz., once a week, and up to 5 injections altogether in single doses of 5 to 10 c.c. In every case the symptoms were mitigated within 2 to 3 weeks, while no fresh attacks occurred. Even though the author does not consider the value of gelatin medication to be conclusively established by these cases, he will continue its use in the future.

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de Bra, Dissertation, Berlin 1910.

Nohl, Dissertation, Berlin 1910.

Finkelstein, Allgemeine medizinische Zentralzeitung 1911, p. 174.

The treatment of aneurysms with gelatin injections has been recently again brought forward by le Dentu and A. Robin. Le Dentu completely cured 2 cases by giving in the one case 7, and in the other case 10 injections. He therefore considers that this method is preferable to surgical procedure. He regards 100 c.c. of a 2 p.c. gelatin solution as the smallest dose, and 200 c.c. to be the normal dose. Robin has also seen the best results following treatment with gelatin.

Gastric ulcers form another indication for gelatin injections, for, according to M. Tollkühn, the gelatin acts as a haemostatic. Subcutaneous application is of most use, rectal infusion is less effective, but in certain cases even the internal administration may be of value. Tollkühn assumes that the gelatin acts by causing thrombosis of the small vessels.

In investigating the value of gelatin injections in the functional examination of bone-marrow, A. v. Decastello and A. Krjukoff came to the following conclusions: The subcutaneous injection of 40 c.c. of Merck's gelatina sterilisata offers a convenient means of bringing about considerable leucocytosis in individuals with normal blood. Besides the neutrophile leucocytes, usually the large mononuclears, and occasionally also the lymphocytes, take part in the increase, so that the leucocytosis is due to all three forms of blood cells. In a series of different pathological conditions, such as diseases of the bone-marrow, typhoid, paratyphoid, malaria, cachexia of cancer and tuberculosis, the authors were able to demonstrate the diminution or loss of the capacity for reaction of the bone-marrow. Thus gelatin injections may be used as a simple method for testing the function of the bone-marrow.

J. B. Studzinski reports upon the question of the effect of subcutaneous injections of gelatin in disease of the kidneys. According to him, the usual doses are harmless in chronic interstitial and chronic parenchymatous nephritis; they only occasionally cause a transient increase in the amount of albumin and of formed elements in the urine. On the other hand, in the presence of parenchymatous hæmorrhage

Dentu, Bulletin médical 1911, No. 12.

Robin, British Medical Journal 1911, I., p. 561.

Tollkühn, Medizinische Klinik 1911, p. 1073.

Decastello-Krjukoff, Medizinische Klinik 1911, No. 6 and 7.

Studzinski, Zeitschrift für klinische Medizin 1911, Vol. 73, No. 4.

of the kidneys, they cause an increase in the hæmorrhage, and the author therefore considers them to be contra-indicated in these cases.

### Glutannin.

This new compound of albumin and tannin, according to Devaux, is prepared from tannic acid and the soluble albumin obtained from wheat flour. In the decomposition of the preparation in the intestine, this vegetable albumin is set free; it is said to possess the advantage, in contra-distinction to animal albumin, of undergoing no complicated disintegration in the lower intestine and of thus not giving rise to products of decomposition which irritate the intestine.

Devaux used glutannin in tuberculous enteritis and was well satisfied with its action. He administered it 3 to 5 times a day in doses of 2 to 3 tablets (of 0.3 gramme [5 grains]), which the patient was told to chew before swallowing. This medication had so far a favourable effect on the diarrhœa in that it became less severe and less frequent. The patient's subjective troubles also disappeared. In simple, non-tuberculous intestinal catarrh, the drug acts promptly in 1 to 2 days. In one case of severe diarrhœa, however, which the author considered to be due to extensive arterio-sclerosis of the mesenteric vessels, it failed, as had all other remedies tried in this case.

### Glycerin.

Before Lister's antiseptic treatment had been introduced into surgery, glycerin was already in use for wounds, and was in the year 1854 warmly recommended by Demarquay. Just as in the last few years new interest has been awakened in various old drugs, such as yeast and kaolin, so F. Rusca seeks to re-introduce glycerin for the treatment of wounds. He has personally used glycerin as a dressing for infected wounds, phlegmon, whitlows and adenitis with good results. The action of glycerin as an antiseptic and of relieving congestion is probably due to its hygroscopic properties, in consequence of which the wound secretions and tissue-juices are

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Devaux, *Münchener medizinische Wochenschrift* 1911, p. 1727.

Rusca, *Korrespondenzblatt für Schweizer Ärzte* 1911, No. 21. —  
*Semaine médicale* 1911, p. 454.

absorbed, their place being taken by fresh juices from the blood. The absorption of the wound secretions by the glycerin cleanses the wounds, while the crusts and necrotic tissues are softened and dissolved, so that the pathogenic bacteria are deprived of their nutrient medium, or it is rendered unsuitable for their growth. There is no danger of poisoning by the employment of glycerin, as it may be absorbed in large amounts without harm. The technique of glycerin dressings also is quite simple; a compress soaked in glycerin is applied to the area in question and covered over with waterproof material. At most a slight burning sensation is experienced shortly after the application, otherwise glycerin dressings are painless and can be painlessly removed. It is usually sufficient to change the dressing twice a day, and if desired an antiseptic may be added to the glycerin. By means of this treatment the wounds rapidly become clean without any symptoms of irritation, suppuration and inflammation disappear, and abscess formation is prevented. Glycerin, however, has no special action on tuberculous ulcerations.

A splendid result is reported by Muktedir in a case of pernicious anæmia. To a patient who, in spite of the usual treatment, was at death's door, he administered at first one tablespoonful of glycerin a day and finally as much as 70 grammes. In a few days the general condition was improved and in a fortnight a considerable improvement in the condition of the blood had taken place. There was a gain in weight, and after a month's treatment with glycerin the patient left the hospital; a fortnight later he reported himself quite well. The author considers this success to have been due to the glycerin. He does not believe that it was due to the laxative action of the drug, for in that case severe essential anæmias could be easily treated.

Glycerin has also proved of use as a bladder laxative. O. Frank, in post-operative paresis of the bladder, injected 15 to 20 grammes of glycerin (containing 2 p.c. of boric acid) directly into the bladder without the use of a catheter, and without previously emptying the bladder. An evacuation of urine followed in about a quarter of an hour, and the

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Muktedir, *Deutsche medizinische Wochenschrift* 1911, p. 930.

Frank, *Zentralblatt für Chirurgie* 1911, 14<sup>th</sup> January. — *Revue de thérapeutique* 1911, p. 173.

further evacuations followed spontaneously. Glycerin is said to act in a similar way in all other forms of retention of urine, e. g., in strictures and paralysis. The treatment is not suitable for acute urethritis anterior, as there is the danger of spreading the pathogenic organisms.

### **Glycocoll.**

Glycocoll, or amido-acetic acid\*), a substance which has been known for nearly 100 years, and which was first prepared by Braconnot by boiling together glue and barium hydroxide or sulphuric acid, is now to be used for therapeutic purposes. K. Glaessner several years ago, in a work on the functional examination of normal and pathological livers, made the observation that various amido-acids, even in small doses, were capable of producing considerable diuresis. Possibly these acids are converted in the liver into urea, which is known to possess a diuretic action. In this way the diuretic action of these acids might be explained. The author considered amido-acetic acid to be suitable for medicinal use, as it is readily soluble in water and has a pleasant taste. According to recent investigations by this author\*\*), using this acid in the healthy and the ailing, the drug produces diuresis in cases of cardiac and hepatic congestion. In some cases of nephritis, also, its diuretic effect is satisfactory. Glycocoll is specially suitable in liver affections with oliguria. In severe cardiac congestion it renders good service in conjunction with cardiac tonics (digitalis). Its action as a diuretic is distinguished by the fact that not only is the water of the urine increased in amount, but that there is also an increase in the solids, as is shown by the specific gravity, the percentage of urea and of chlorides, and the lowering of the freezing point of the urine.

As glycocoll is perfectly harmless, which cannot be said of all diuretics, it may be recommended for trial. The action of the preparation is most evident after prolonged administration in cases of congestion of the portal system, and for

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\*) Compare Merck's Report 1908, p. 215.

Braconnot, *Annales de chimie et de physique* (2<sup>nd</sup> Series) Vol. 13, p. 114.

Glaessner, *Zeitschrift für experimentelle Pathologie und Therapie* 1907, Vol. 4, p. 336.

\*\*) Glässner, *Therapeutische Monatshefte* 1911, p. 479.

this reason Glaessner considers glycooll to be specially indicated for such cases. The author has so far fixed the dose at 5 grammes (75 grains) a day. This amount may be dissolved in 150 grammes (5 oz) of water and administered during the course of the day.

#### **$\alpha$ -Glycoheptoic Acid Lactone.**

G. Rosenfeld, F. Rosenfeld and J. Pringsheim report upon a new drug which seems destined to play a certain rôle in the treatment of diabetes mellitus. This is a substance belonging to the group of heptoses, the lactone of  $\alpha$ -glycoheptoic acid. This body has a sweetish taste, is readily soluble in water, does not reduce metallic oxides and is lævo-rotatory.

According to the investigations of Rosenfeld, lactone is readily absorbed in the animal and human organism, without giving rise to antiketoic action. It is also completely used up by the diabetic, and frequently reduces the glycosuria. Only occasionally the lactone medication is said to give rise to diarrhœa, but the preparation appears to cause no other secondary effects.

Even though no explanation of the action of lactone has as yet been advanced, the action itself justifies the further trial of this drug. Rosenfeld recommends daily doses of 10 to 30 grammes ( $\frac{1}{3}$ —1 oz) to be administered in tea, an interval being allowed after one or more days. In testing Rosenfeld's statements, Pringsheim found that the sugar disappeared from the urine in 6 cases of glycosuria, and he thus confirmed Rosenfeld's results. His results show that a diabetic patient is able to use up as much as 30 grammes (1 oz) of lactone a day, while with daily doses of 40 grammes ( $1\frac{1}{3}$  oz) or more a small amount is occasionally excreted in the urine. But even 50 grammes ( $1\frac{2}{3}$  oz) of the preparation are as a rule well borne and only in a patient with carbohydrate hunger and acetonuria did the author observe the occurrence of moderate diarrhœa. On the other hand, he was able to obtain a favourable effect of lactone on acetonuria due to diabetes or to carbohydrate hunger, although this effect was not reg-

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Rosenfeld, Berliner klinische Wochenschrift 1911, p. 1313.

Pringsheim, Therapeutische Monatshefte 1911, p. 657.

ular. But the new drug is unsatisfactory owing to the absence of a lasting action, for its good effect in 3 out of 5 cases was only apparent during the first few days and could not be obtained again, even by increasing the dose. Only in one case was tolerance increased by lactone medication, which remained on discontinuing the drug.

F. Rosenfeld reports three cases. In no case was there an increase of sugar when 20 grammes ( $\frac{2}{3}$  oz) of lactone a day were given, while in 2 cases a slight decrease was observed. Diarrhœa occurred in all the cases. No effect was observed on the excretion of acetone and aceto-acetic acid.

### **Gonosan.**

In acute gonorrhœa, especially in the treatment of the inflammatory stage, G. H. Day obtained excellent results by the daily administration of 4 to 8 capsules of gonosan. Like many other\*) authors, he has also confirmed the marked anæsthetising and sedative action of the preparation, which is specially valuable in painful micturition and erections; and also that it reduces secretion, and, combined with suitable diet and rest, aids in the prevention of complications. It is, therefore, according to Day, worthy of special consideration. Scherber arrived at similar conclusions; he prescribed it, together with argonin and protargol, in order to reduce the secretion and alleviate the pain. In his experience it is also indicated in urethritis posterior, which is always accompanied by inflammation of the prostate, provided there be no terminal hæmaturia.

A. Siegfried, who has for years used gonosan for acute gonorrhœa, has found that the complications and pain of the initial stage are reduced to a minimum by the use of this drug. Like S. Boss, he warns against the employment of less valuable substitutes, the composition and action of which do not at all correspond with that of gonosan.

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Rosenfeld, Deutsche medizinische Wochenschrift 1911, p. 2189.

Day, Medical Progress 1910, No. 295.

\*) Compare Merck's Reports 1902—1910.

Scherber, Ärztliche Reformzeitung 1911, No. 5.

Siegfried, Berliner Klinik 1911, No. 280.

Boss, Berliner Klinik 1911, No. 280.

### Guaiacol Preparations.

N. Moldaresco used pure crystalline guaiacol internally and externally, not without success, in the treatment of various forms of leprosy. Internally he prescribed it in the form of pills: Rp. Guaiacol. 5 grammes (75 grains), Eucalyptol. 2 grammes (34 min.). Ext. glycyrrh. q. s. ut. ft. pil. No. 50. At first 2 pills are given every morning and evening and the dose is gradually increased until 10 pills are taken daily, corresponding to 1 gramme (15 grains) of guaiacol. After a fortnight an interval of 5 days is allowed. As the guaiacol given internally is in part excreted by the skin, Moldaresco assumes that a direct action on the infiltrations of the skin is thus rendered possible. The action is enhanced by the external application of the drug, for which purpose the guaiacol is applied several times a day by means of a brush to the diseased areas of the skin, and the parts treated are covered with cotton wool and a bandage. Guaiacol is very rapidly absorbed through the skin. According to the author, it gives rise to no cutaneous irritation if it is pure, but aids in checking the suppuration, causing the crusts to fall off and the ulcers to cicatrise.

In order to decide which of the newer guaiacol preparations is best absorbed and most suitable for therapeutic purposes, Th. Knapp suggests that quantitative tests of the urine should be carried out for determining the presence of esters of sulphuric acid and glycuronic acid, as the absorbed guaiacol appears combined with these in the urine and thus renders a comparison of the activity of the different guaiacol preparations possible. By carrying out investigations of this nature he obtained results which still await confirmation by others. He asserts that only a small amount of guaiacol carbonate is absorbed, the greater part passing unchanged through the intestine, that potassium guaiacol-sulphonate in ordinary doses gives rise to no increase in the glycuronic acid and is therefore inactive, that on the other hand guaiacol-cinnamic ester and guaiacol-glycerin ester are very rapidly decomposed and absorbed in the system. These results certainly do not correspond with the great therapeutic successes obtained by

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Moldaresco, *Klinisch-therapeutische Wochenschrift* 1911, No. 23.

Knapp, *Schweizer Wochenschrift für Chemie und Pharmazie* 1911, No. 17. — *Petersburger medizinische Wochenschrift* 1911, No. 23.

the use of guaiacol carbonate and potassium guaiacol-sulphonate.

Jungbluth, Elkan, F. Dorn and A. Pollak have expressed themselves well satisfied with the value of guaiacose (a solution of calcium guaiacol-sulphonate in liquid somatose). On the whole these authors agree that the general condition, the weight, the night sweats and the cough of phthisical patients are favourably influenced by the use of guaiacose\*). Dorn considers it to be non-toxic and would have it prescribed in larger doses than has hitherto been customary. In the mildest cases of illness, at least 4 half tablespoonfuls of guaiacose should be given in the beginning, and the amount rapidly increased to 3 or 4 tablespoonfuls a day. In a severe case 3 tablespoonfuls a day should be given from the beginning. The taste of guaiacose is, according to Pollak, very peculiar and difficult to define, for which reason some patients refuse to take the drug, but most patients take it gladly or soon become accustomed to the taste. Apart from this, the author has never observed troublesome by-effects.

Hexamecol is the name of a new guaiacol preparation, a combination of guaiacol and hexamethylenetetramine. One gramme of this preparation contains 0.65 gramme of guaiacol. It forms a white powder, which is to be rubbed into the painful parts by means of rubber gloves in doses of 2 grammes (30 grains) once or twice a day. According to Lüdín, it usually gives satisfaction in the pains of pleurisy, spondylitis, pulmonary tuberculosis and itching affections of the skin.

L. Nürnbergger denies the specific influence on tuberculosis of guaiacol-arsenic, recommended by Burow against tuberculosis; for he was able to demonstrate that relatively large additions of guaiacol and potassium arsenite, either separately or combined, do not prevent the growth of tubercle

Jungbluth, *Medizinische Klinik* 1911, No. 7.

Elkan, *Therapie der Gegenwart* 1911, No. 4.

Dorn, *Allgemeine medizinische Zentralzeitung* 1911, No. 1.

Pollak, *Medizinische Blätter* 1910, No. 47.

\*) Compare Merck's Report 1910.

Lüdín, *Münchener medizinische Wochenschrift* 1911, No. 23.

Nürnbergger, *Münchener medizinische Wochenschrift* 1911, p. 2669.

Burow, Merck's Report 1910, p. 200.

bacilli on glycerin-agar, and that the two drugs did not in the slightest degree influence inoculated tuberculosis in rabbits or guinea-pigs.

### Gynoval.

Gynoval, according to the communications of O. Aronsohn, is on the market in the form of ordinary gelatin capsules and in so-called gelodurat capsules, containing 0.25 gramme of the preparation. As the gelodurat capsules pass unaltered through the stomach and are not dissolved until they reach the intestine, they are especially indicated for the administration of gynoval to sensitive patients who otherwise show signs of nausea and vomiting after taking the drug. The favourable effect of gynoval\*) observed by others in functional nervous disturbances was confirmed by the author in a series of cases. Thus in a case of Menière's disease in a man aged 57, the attacks of vertigo were most favourably influenced by the preparation. In a man aged 63, who remained unaffected by any form of suggestion, and who suffered from aphasic disturbances following an apoplectic attack, the insomnia was so far improved that sleep occurred sooner and lasted longer. In this case, however, the author was obliged to give 1 to 1.5 grammes of gynoval at night time. On the other hand, in some cases of nervous insomnia 0.5 gramme procured sufficient sleep, and in most cases 1 gramme. In two cases the female patients reported that menstrual pain had ceased after gynoval medication, and in a number of cases of neurasthenia, hysteria (hysterical cough), phobias, nervous gastric and intestinal symptoms, and cardiac palpitation, gynoval had an undoubted calming effect, if given in daily doses of 1 to 1.5 grammes.

M. Weissbart draws attention to the beneficial action of gynoval in secondary nervous disturbances, such as the troubles of menstruation and disturbances during the climacteric. It is also useful in the troubles of pregnancy, exerting a favourable influence upon the vomiting, the headache and the giddiness.

Aronsohn, Medizinische Klinik 1911, p. 1389.

\*) Compare Merck's Reports 1909 and 1910.

Weissbart, Heilkunde 1910, No. 12.



and Blaye, H. Moutot, Dive, Ravasini, Balzer and Hallopeau.

Schoull reports upon 8 cases of syphilis in which hectine and hectargyre were of service. He injected both drugs intramuscularly, in series of 10 injections, giving daily 0.1 to 0.2 gramme ( $1\frac{1}{2}$ —3 grains). He never observed a local reaction and only with hectargyre occasionally slight stomatitis.

Nor did Selenew observe any secondary effects. In his experience hectine acts in a similar way to salvarsan, for the sclerosis disappears, the ulcers heal, the roseola fades, papules are absorbed, erythematous angina disappears, spirochetes disappear from the blood and the Wassermann reaction is occasionally weaker after only 2 to 3 injections, and with further treatment becomes negative. In the primary stage, combined with iodine, hectine prevents, though not always, the outbreak of generalised syphilis and the development of a positive Wassermann reaction.

According to Dive, a rapid action of hectine is specially observed in the primary period of hard chancre, in the secondary stage in iritis, affections of the skin and mucous membranes, and in the tertiary stage in ulcerative and gummatous symptoms, and in nervous phenomena.

Ravasine and Moutot express themselves but little satisfied with the abortive cure with hectine inaugurated by Hallopeau. They did not have a single successful case. Hallopeau himself, on the other hand, is convinced of its value, even in his recent communication\*).

The absence of secondary effects pointed out by most authors may possibly be due to the comparatively small doses which have so far been employed. Nearly all authors suggest 0.1 to 0.2 gramme ( $1\frac{1}{2}$ —3 grains) for a daily dose, whereas of atoxyl, which is chemically nearly related to hectine, doses of 0.5 gramme ( $7\frac{1}{2}$  grains) were usually prescribed. Moreover

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Moutot, *Annales des maladies vénériennes* 1911, Vol. 6, No. 9.  
Dive, *Dissertation* Paris 1910. — *Revue internationale de médecine* 1911, p. 160.

Ravasini, *Münchener medizinische Wochenschrift* 1911, p. 81.

Balzer, *Presse médicale* 1911, p. 1059.

Hallopeau, *Bulletin général de thérapeutique* 1911, 13<sup>th</sup> February.

*Bulletin de l'academie de médecine* 1911, Nr. 3.

\*) Compare Merck's Report 1910.

Gaucher, Ballet and Hirschmann, in using small doses of hectine observed disturbances of vision and of hearing, which show that caution is necessary. The eyes should always be tested before commencing a hectine cure. Dive mentions as the only contra-indication syphilitic diseases of the eyes, especially if the optic nerve be affected. He has also obtained good results at the commencement of tabes, whereas he considers the action of hectine in paralysis to be doubtful, even if large doses of 0.5 to 0.7 gramme ( $7\frac{1}{2}$ —11 grains) are employed.

Trials have also been made by Marie and Bourilhet in general and progressive paralysis. Using doses of 0.1 to 0.2 gramme ( $1\frac{1}{2}$ —3 grains) of hectine or hectargyre in 6 cases, they once observed the disappearance and in two instances the diminution of the Wassermann reaction, but they consider a cure to be impossible. They believe, however, that hectine treatment may bring about a diminution of the severe symptoms of meningo-encephalitis and remissions in progressive paralysis.

Hectine treatment would appear to offer a prospect of success in malaria, if the statements of Roques are confirmed; by giving intramuscular injections he caused the disappearance of the parasites from the peripheral blood and a rapid fall of temperature. He gave 0.1 to 0.2 gramme ( $1\frac{1}{2}$ —3 grains) of hectine. Doses of 0.25 gramme (4 grains) are said to be no more effective, even though in his experience they are well borne\*).

### Hedonal.

Intravenous hedonal anæsthesia was last year discussed by A. P. Jeremitsch, J. Krzizewsky, L. Albinsky,

Marie-Bourilhet, Bulletin général de thérapeutique 1911, No. 8.

-- Revue de thérapeutique 1911, p. 160.

Roques, Presse médicale 1911, p. 664.

\*) Hectine, as is well known, is the sodium salt of benzo-sulpho-p-aminophenylarsonic acid, and was first prepared and therapeutically tested, not by Mouneyrat, but in the Speyer House in Frankfort o. M. A method of preparing this acid has been patented in Germany since 1906.

Jeremitsch, Deutsche Zeitschrift für Chirurgie 1911, Vol. 108, No. 5—6.

Krzizewsky, Russkij Wratsch 1911, No. 13.

Albinsky, Russkij Wratsch 1911, No. 13.

Fedoroff and Lytschkowski\*). According to these authors, the advantages of this method of anæsthesia, which had been described by others, were on the whole confirmed. Jeremitsch, who injected 300 to 1100 c.c. of a 0.75 p.c. hedonal solution peripherally into the median vein, obtained satisfactory results in 65 cases. The special advantages of this method consist in good cardiac action, regular breathing and absence of excitement and post-operative symptoms. The infusion of 70 c.c. of hedonal solution per minute produces anæsthesia in about 5 to 8 minutes. Fedoroff adopted the intravenous application of hedonal in 530 cases. He had no fatal case and only in 8 cases did he observe the cessation of breathing and slight cyanosis. Usually the cessation of breathing is caused by too rapid infusion, for which reason the author suggests that in feeble patients 50 to 60 p.c. of the hedonal solution referred to should be infused per minute, and in strong persons and alcoholics 100 c.c. In his experience 0.04 gramme ( $\frac{2}{3}$  grain) of hedonal per kilogramme of body-weight are required for anæsthesia. The method may also be employed for operations on persons suffering from renal disease and arterio-sclerosis.

Lytschkowski criticises the technique and the apparatus suggested by Jeremitsch. He describes an apparatus by means of which the temperature of the solution can be regulated, and the rapidity of infusion controlled, while the amount of solution used can be checked.

### Heroin.

As is well known, Dreser, based on his pharmacological experiments, made the statement that heroin causes a marked decrease in the rate of respiration, prolongation of the inspiratory period and deeper inspiration. This action of strengthening respiration was partially or entirely confirmed

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Fedoroff, 40. *Versammlung der deutschen Gesellschaft für Chirurgie zu Berlin, April 1911*, communicated by W. Klink, *Therapie der Gegenwart* 1911, p. 268. — *Allgemeine medizinische Zentralzeitung* 1911, p. 305.

Lytschkowski, *Petersburger medizinische Wochenschrift* 1911, p. 209.

\*) Compare Merck's Report 1910.

Dreser, *Archiv für die gesamte Physiologie*, Vol. 72, p. 80. — Merck's Report 1898, p. 98.

by various observers, but contradicted by others\*); the action mentioned was even attributed not to heroin alone, but also to other derivatives of morphine and to morphine itself. B. von Issekutz has therefore recently investigated the action of heroin, codeine, dionin and morphine on respiration and came to the following conclusions: there is no qualitative difference between morphine, codeine, dionin and heroin as regards their action on respiration. Each of these substances diminishes the number of inspirations, the volume, the energy and the power of the respiration of a normally breathing animal. But if the animal breathes superficially, then each of the substances named increases the volume, the energy and the power of the respiration.

P. Duhem has pointed out that heroin is not suitable for use in the cure of the morphine habit, for in his experience heroinism is more difficult to treat than is morphinism. He confirms this statement in a recent communication. In his opinion, heroin is not only no less toxic than morphine, but the symptoms which appear in heroinomaniacs, such as weakness, prostration, leaden complexion, etc., are more marked than is the case in morphinomaniacs. The deprivation of heroin causes the appearance of torpor, decrease in the rate of respiration, poor blood regeneration and the danger of severe respiratory syncope, which may supervene without any premonitory symptoms. But whereas the cardiac syncope caused by the deprivation of morphine is successfully combated by injections of morphine, syncope appearing in the course of deprivation of heroin must not be treated by heroin, but it is better to resort to the use of morphine. The latter also offers the best protection against the respiratory syncope of heroinomania.

### Hexamethylenetetramine. (Urotropine.)

This well known urinary antiseptic is, according to Miller, eliminated after internal administration not only in the urine,

\*) Compare Merck's Reports 1898, 1899 and 1900.

Issekutz, Archiv für die gesamte Physiologie, Vol. 142, p. 255.  
Duhem, Progrès médical 1907, No. 8. — Merck's Report 1907, p. 123.

Duhem, Journal des praticiens 1911, No. 15. — Klinisch-therapeutische Wochenschrift 1911, p. 611.

Miller, Journal of the American Medical Association 1911, 10<sup>th</sup> June, p. 1718.

but also by the mucous membrane of the upper respiratory passages, and it thus also acts as an antiseptic in these parts. He therefore recommends it in diseases of the upper respiratory passages, in large daily doses of 4 grammes (60 grains). The maximum daily dose given in the German Pharmacopœia is only 3 grammes (45 grains). The author is of opinion that only large doses exert a sufficient action and that they are harmless, provided they are taken in a large amount of water. In this way irritation of the bladder is prevented. In poliomyelitis, also, the use of hexamethylenetetramine might prove beneficial, for S. Flexner and P. F. Clark have shown in experiments on animals that after the internal administration of urotropine the experimental transmission of the disease either fails or else the period of incubation is considerably prolonged. Further, A. Chauffard refers to the value of urotropine in typhoid fever and acute biliary infections, the effect being due to its elimination by the bile. He considers the drug to be the most effective internal antiseptic, capable of the greatest diffusion, and should be administered in single doses of 0.5 to 1 gramme ( $7\frac{1}{2}$ —15 grains), and in daily doses of 2 to 3 grammes (30—45 grains). The author considers it inadvisable to attempt to render the bile sterile by a single administration of 5 grammes (75 grains).

Urotropine may, according to F. C. Shatuck, be used as a prophylactic against pneumococcal empyema in cases of croupous pneumonia. But his experiments in this direction with the internal administration are so far not conclusive. He observed, however, that other complications, such as otitis or pericarditis, did not occur, and this may have been due to the urotropine.

Givasan, a tooth paste\*) containing hexamethylenetetramine, has been reported upon by G. Nobel, O. Fraenkel, Krakowski, Lamberti, Lechtmann, Lewinski,

Flexner-Clark, *Nouveaux remèdes* 1911, p. 318.

Chauffard, *Semaine médicale* 1911, 1. 109.

Shatuck, *Boston Medical and Surgical Journal* 1911, 1, p. 842.

\*) Compare Merck's Report 1909.

Nobel, *Deutsche zahnärztliche Wochenschrift* 1911, No. 17.

Fraenkel, *Deutsche zahnärztliche Wochenschrift* 1911, No. 22.

Krakowski, *Kronika Dentystyczna* 1911, No. 4.

Lamberti, *Deutsche zahnärztliche Wochenschrift* 1911, No. 37.

Lechtmann, *Der praktische Arzt* 1911, No. 2.

Lewinski, *Deutsche zahnärztliche Wochenschrift* 1911, No. 28.

Ritter and Fritzsche. The effect of this preparation is due to the liberation of formaldehyde from the hexamethylenetetramine by the action of the saliva. According to the unanimous opinion of these authors, givasan paste has not only proved useful as a preparation for cleaning the teeth in normal conditions of the mouth, but has also been of good service in various diseased conditions of the gums, such as gingivitis, stomatitis, formation of tartar, etc. The preparation is of special value in the treatment and prophylaxis of stomatitis mercurialis.

Another new preparation containing hexamethylenetetramine, hexamecol, has already been described in the article on "Guaiaicol Preparations".

### Histopin.

This preparation, according to A. von Wassermann, consists of the immunising substances of living staphylococci, obtained from the latter by extraction with water; in order that it may keep, a protective colloid — a dilute solution of gelatin — is added, together with 0.5 p.c. phenol. Histopin is perfectly sterile, and does not contain any living staphylococci. As much as is considered requisite may be applied to the skin for weeks, and in certain staphylococcic infections it has a local immunising effect. This fact, which was confirmed by Wassermann in experiments in animals, induced R. Ledermann to test histopin on the human organism. According to him, certain forms of furunculosis are specially suitable for treatment with histopin, particularly in cases the origin of which can be traced wholly to staphylococci. This applies not only to those characteristic furuncles in a narrow sense which originate by the entrance of the specific organisms into the hair follicles, and lead to more or less extensive, superficial or deeper, follicular and perifollicular inflammations, but also to those superficial forms, so troublesome to the sufferer, known as impetigo staphylogenes Bockhart, and characterised by the frequent recurrence of pustules. Small furuncles, or those which are just developing, are painted with pure histopin, or with a 25 to 50 p.c. histopin ointment;

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Ritter, Deutsche zahnärztliche Wochenschrift 1911, No. 26.

Fritzsche, Deutsche Monatsschrift für Zahnheilkunde 1911, No. 9.

Wassermann, Medizinische Klinik 1911, p. 479.

Ledermann, Medizinische Klinik 1911, p. 480.

in the case of large furuncles small incisions are made, and the pus is removed by means of a Bier's suction glass, and thus an entrance is established for the drug. Histopin is of special importance in the prophylaxis of furunculosis, because it is capable of preventing recurrences. For the greatest difficulty in the treatment of furunculous affections is, as a rule, not the cure of the separate furuncles, but the prevention of fresh outbreaks. For this purpose Wassermann's staphylococci extract and gelatin is said to be specially valuable. Ledermann succeeded, in several cases which had lasted for years with continuous recurrences, in stopping the formation of furuncles by painting extensive and apparently healthy areas of skin with histopin.

### Hydrochloric Acid.

Last year I referred to the successes which were obtained by Beebe and Rüdich by administering hydrochloric acid in pernicious anæmia. A. C. Croftan had just as favourable results with the use of this acid; he prescribed over-feeding with albumen and large doses of hydrochloric acid in 3 cases of pernicious anæmia. He prescribed 15 to 20 drops of 40 p.c. hydrochloric acid (sp. gr. 1.19<sup>\*)</sup> to be taken a quarter to half an hour after every meal (3 to 4 times daily), so that altogether 90 to 160 drops were given during the day. The use of this acid, in the author's experience, has no ill effects, but brings about a rapid improvement in nutrition and general health; the condition of the blood is improved in the course of 3 to 4 weeks, and if diarrhœa is present, it is stopped. According to Behrendt, the great weakness and loss of weight which is present in all cases of achylia gastrica is caused by the diarrhœa. Croftan believes that a specific action may be attributed to hydrochloric acid, for deficiency of hydrochloric acid in the stomach is detrimental to the functions of the stomach, to metabolism

Beebe-Rüdich, *Klinisch-therapeutische Wochenschrift* 1910, p. 453.  
Croftan, *Journal of the American Medical Association* 1910, p. 593 (13<sup>th</sup> August). — *Münchener medizinische Wochenschrift* 1911, p. 774.

<sup>\*)</sup> Naturally suitably diluted and with proper precautions.

Behrendt, *Journal of the American Medical Association* 1910, p. 593 (13<sup>th</sup> August). — *Münchener medizinische Wochenschrift* 1911, p. 774.

and probably also to the formation of blood corpuscles. But Croftan is unable to give an exact scientific explanation of the action of hydrochloric acid. As this treatment is so simple and harmless, its further trial, especially in severe cases, seems advisable.

The use of hydrochloric acid treatment in gout\*) is confirmed by the experiences of J. J. Schmidt. Falkenstein, who inaugurated this method of treatment, argued that metabolism was so much influenced by the prophylactic employment of hydrochloric acid that any fresh deposition of uric acid was prevented. This assumption was supported by the communications of Loghem, Silbergleit and Solger, so that the advantages of hydrochloric acid treatment over treatment with alkalis were made manifest. Klemperer alone objected to hydrochloric acid treatment, but he only prescribed hydrochloric acid during the attack and not, as Falkenstein advised, as a prophylactic measure. Schmidt, in his own case, diagnosed chronic stomach trouble associated with anacidity, and after an unsuccessful course of baths and mineral waters, together with abstinence from alcohol, he tried for over a year the use of 60 drops (4.5 grammes) (70 min.) of hydrochloric acid (25 p.c.) daily. In spite of these large doses he did not perceive the slightest harmful effect. The result was most striking, for even in the first 3 months of treatment the attacks of gout only lasted for 1 to 2 hours and were free from considerable pain and did not interfere with his professional work. Since this time the author has been free from gout for close upon two years, although he does not trouble about special diet or abstinence from alcohol. He was equally successful with 7 patients suffering from regular gout, whereas the action of hydrochloric acid in chronic, irregular gout, the so-called atypical form, although not so rapid, was quite satisfactory.

\*) Compare Merck's Report 1904, p. 7 and 1910, p. 67.

Schmidt, Münchener medizinische Wochenschrift 1911, p. 1764.

Falkenstein, Die Gicht und die Salzsäurejodkur, Published by Hirschwald, Berlin 1909. — Klinisch-therapeutische Wochenschrift 1904, p. 59.

Loghem, Archiv für klinische Medizin 1905, p. 416. — Nederlandsch Weekblad 1905, No. 7.

Silbergleit, Therapie der Gegenwart 1906, p. 387.

Solger, Deutsche medizinische Wochenschrift 1910, p. 1546.

Klemperer, Therapie der Gegenwart 1907, p. 425.

No benefit can be expected from the use of hydrochloric acid in chronic rheumatic joint affections and it is therefore the doctor's duty to distinguish these carefully from gout by examination of the blood, X ray examination and testing the purin metabolism. In order to amplify the cure it is well, as suggested by Falkenstein, to take a course of iodine for a few weeks once a year; this is said to bring about an increased elimination of nitrogen and the abstraction of alkalis from the body. He prescribed 80 tablets of iodoglidine to be taken consecutively in the stated time.

Schmidt assumes the action of hydrochloric acid to be as follows: "By means of the large doses of hydrochloric acid introduced large amounts of alkali are withdrawn from the body and the content of uric acid in the blood is kept so constantly low that no hyperuricæmia, and no excretion of uric acid depending therefrom can ensue. Furthermore, the hydrochloric acid appears to have a powerful activating effect on the disturbed fermentation mechanism of the uric acid metabolism, analogous to its influence on the ferments of the stomach and the pancreas; as a consequence, under continuous treatment with hydrochloric acid, the tolerance for food-stuffs containing purin is increased, and the gouty subject, with due observance of the principle of moderation and muscular exercise, may behave like a healthy individual as far as his nourishment is concerned."

### Hydropyrin.

The purity of lithium acetyl-salicylate, which is issued under the name of hydropyrin (L or Grifa), has been questioned on the ground of chemical investigations by Goldmann, Spiegel, Seel and Friederich, who demonstrated that this preparation contained not only the products of decomposition of aceto-salicylic acid, but also a considerable amount of sodium acetyl-salicylate. But later S. Fränkel showed that the commercial product consists chiefly of lithium acetyl-salicylate and only contains traces of the sodium salt, and this is confirmed by the recent investigations of Spiegel. Thus the composition of the preparation has been improved. But

Goldmann, *Berichte der deutschen pharmazeutischen Gesellschaft* 1910, p. 9.

Spiegel, *Deutsche medizinische Wochenschrift* 1911, p. 458.

Seel-Friederich, *Berliner klinische Wochenschrift* 1911, p. 1258.

Fränkel, *Deutsche medizinische Wochenschrift* 1911, p. 1750.

it still appears to undergo decomposition in the presence of air, for Spiegel, in the preparation analysed by him, found about 1 p. c. of acid (calculated as acetic acid).

H. Boruttau studied the behaviour of hydropyrin in the organism and demonstrated in animals that salicylic acid is split off from the preparation in the intestines and the blood, and that it is excreted in the urine as soon and as completely as occurs after the ingestion of salicylic acid and the salicylates. The toxicity of hydropyrin is said to be considerably less than that of sodium salicylate. According to Tippelskirch, the action of hydropyrin on the kidneys is less harmful than that of aspirin, for the majority of his patients were able to take 5 to 6 grammes (75–90 grains) of the preparation on several consecutive days without the least trace of albumin or of casts appearing in the urine. In some cases, in which a few casts were found, they disappeared within a few days. Otherwise the author considers hydropyrin to be therapeutically of about equal value to aspirin. S. Möller came to a similar conclusion, but J. Biro found hydropyrin to be inferior to aspirin in its action. The secondary effects of the drug are also the same as those of aspirin, except that it causes less abdominal pain. Further, the author points out that on account of its ready solubility in water it can be administered per rectum, a method specially suitable in polyarthritis.

The indications for hydropyrin are, according to F. Loeb, muscular and articular rheumatism, neuralgia, influenza, febrile diseases, migraine, pneumonia, dysmenorrhœa, and bronchitis. The usual form of administration is in tablets of 0.5 gramme ( $7\frac{1}{2}$  grains) (1 tablet to be taken every 1 to 2 hours), or in solution 5:150, of which one tablespoonful corresponds to 0.5 gramme ( $7\frac{1}{2}$  grains) of hydropyrin.

### Hydroquinine.

Hydroquinine (methyl-hydrocupreine) is obtained from the mother-liquor in the manufacture of quinine. It occurs as a white,

Spiegel, Deutsche medizinische Wochenschrift 1911, p. 1751.

Boruttau, Deutsche medizinische Wochenschrift 1911, p. 73.

Tippelskirch, Therapie der Gegenwart 1911, p. 392.

Möller, Berliner klinische Wochenschrift 1911, p. 255.

Biro, Pester medizinisch-chirurgische Presse 1911, No. 13–14. —

Zentralblatt für die gesamte Therapie 1911, p. 267.

Loeb, Zentralblatt für die gesamte Therapie 1911, p. 337.

crystalline powder melting at  $168^{\circ}\text{C}$ . Its chemical formula differs from that of quinine in that it contains 2 extra atoms of hydrogen in the molecule; it has thus the formula  $\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}_2(+2\text{H}_2\text{O})$ . In its properties it is very similar to quinine; thus it is sparingly soluble in water, readily soluble in alcohol, ether and chloroform, and gives the thalleioquin reaction. The hydrochloride,  $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2\cdot\text{HCl}\cdot 2\text{H}_2\text{O}$ , forms crystals which are readily soluble in water and alcohol\*).

As quinine has no marked action on trypanosomes, J. Morgenroth and L. Halberstädter tested in animals the power of some of the derivatives of quinine of destroying trypanosomes; they found that hydroquinine hydrochloride, given subcutaneously in doses corresponding to those of quinine, in almost all cases caused the total disappearance of the trypanosomes from the circulation, which is not the case with quinine. This marked superiority is also possessed by the nearest homologue of hydroquinine, ethyl-hydrocupreine, whereas hydrochloro-isoquinine, also investigated by the same observers, proved without effect even when given in the largest safe doses. In pneumococcal infection Morgenroth and R. Levy were unable to obtain a prophylactic action in animal experiments either by subcutaneous injections of quinine or by feeding with hydroquinine, but ethyl-hydrocupreine showed a definite action, so that there seems a prospect of its therapeutic employment in pneumococcal infection\*\*).

### Hyperol.

The combination of urea and hydrogen peroxide,  $\text{CO}(\text{NH})_2)_2\cdot\text{H}_2\text{O}_2$ , first prepared by S. Tanatar, is now on the market under the name of "hyperol". According to F. Kubàt, this preparation is an odourless, crystalline, white powder, having a salty taste and an acid reaction. On heating it melts and breaks up into water, oxygen and ammonia. It is soluble

\*) Compare Hesse, *Berichte der deutschen chemischen Gesellschaft Berlin* 1882, Vol. 15, p. 856 and *Liebigs Annalen* 1887, Vol. 241, p. 255.

Morgenroth-Halberstädter, *Berliner klinische Wochenschrift* 1911, p. 1558.

Morgenroth-Levy, *Berliner klinische Wochenschrift* 1911, p. 1560.

\*\*) Compare the article on "Ethyl-hydrocupreine" in this Report. Tanatar, *Journal of the Russian Physical-Chemical Society, Odessa* 1908, Vol. 40, p. 376.

Kubàt, *Pharmazeutische Praxis* 1911, p. 398.

1 in 2.3 of water with the development of heat, and 1 in 7.5 of alcohol; it is insoluble in chloroform. Ether decomposes it into its components, urea and hydrogen peroxide, of which only the latter dissolves in the ether. Theoretically, hyperol should contain 36.05 p.c. of  $\text{H}_2\text{O}_2$ . According to Kubàt, it contains very nearly this amount, for the commercial product contains 34 to 34.5 p.c. of  $\text{H}_2\text{O}_2$ . According to Milbauer, hyperol contains 0.08 p.c. of citric acid, which acts as a preservative, as the carbamide-hydrogen-peroxide itself is not stable. The preparation is, according to the author, suitable for analytical purposes in the place of hydrogen peroxide.

### Ichthyol.

Ichthyol has been found a valuable drug in tuberculosis. This is confirmed by W. S. Barnes, after using ichthyol internally for a number of years with satisfactory results in the early stages of tuberculosis and in bronchitis. In his opinion, the action of the preparation is due to its antiseptic properties and to its vaso-constrictive effects. Further, it acts as a stimulant, increasing the gastric secretion; it improves the appetite and promotes the assimilation of the food. If, therefore, the appetite be not improved at the very commencement of ichthyol medication, according to Barnes, the further administration of the drug is useless. The author prefers ichthyol in the fluid form for internal administration, e. g., a solution of the drug in peppermint water and liquorice juice, which is best taken after meals. Ichthyol tablets of 0.3 gramme (5 grains) are also useful. Barnes used to give 1.25 grammes (20 grains) as a daily dose.

Ichthyol is also useful internally in pertussis. Naamé obtained excellent results with the following prescription:

Rp. Ichthyol	10.0 grammes ( $\frac{1}{3}$ oz)
Glycerin.	20.0 grammes ( $\frac{2}{3}$ oz)
Spirit. meliss. co.	2.0 grammes (34 min.)
Spirit. menth. pip.	2.0 grammes (34 min.)
Ol. amygdal. amar. ver.	gtts. III.
Syrup.	ad 100.0 grammes ( $3\frac{1}{3}$ oz)

Milbauer, *Chemiker-Zeitung* 1911, p. 871.

Barnes, *Medical Record* 1911, 21<sup>st</sup> January. — *Merck's Archives* 1911, No. 3. — *Revue de thérapeutique* 1911, p. 309.

Naamé, *Bulletin général de thérapeutique* 1911, p. 238.

Of this mixture children of 1 year are given 4 to 6 teaspoonfuls, children up to 2 years, 3 to 4 dessertspoonfuls, children of 3 to 4 years, 4 to 5 dessertspoonfuls, and older children 4 to 5 tablespoonfuls.

In prostatitis, when the acute stage is over, G. Hahn prescribes ichthyol suppositories of the following composition:

Rp. Ichthyol	2.0 grammes (30 grains)
Ext. bellad.	0.1 gramme ( $1\frac{1}{2}$ grains)
Ol. theobrom. q. s. ut f. supposit. No. X.	

Sig.: One to be introduced twice a day.

A further method of using ichthyol in furunculosis is advocated by F. Bruch. According to his instructions, the hair in the neighbourhood of the furuncle is removed with a razor and the whole of the red area is painted with pure ichthyol. For this purpose a small glass spatula is used, such as is employed in ophthalmic practice; after each application of ichthyol it is cleansed and disinfected. Directly over the layer of ichthyol a piece of plaster (leucoplast) is applied, covering a larger area than does the ichthyol. With this dressing the pain rapidly disappears; even with large furuncles the patient is usually free from pain in 3 to 4 hours. When the dressing is changed on the following day, the pus is removed by means of a plug of cotton wool dipped in benzine and the treatment already described is repeated. This is continued until the suppuration ceases. It not only leads to excellent cosmetic results, but also allows the patient to follow his occupation.

For the treatment of weeping eczema of the leg and eczema of the skin, Dreuw recommends a so-called cement-paste which hardens on the skin in the course of 24 hours, forming a grey, cement-like, porous layer. It consists of ichthyol 5 to 10 grammes, sulphur 10 grammes and pasta Lassar q. s. ad 100 grammes, and has an absorbent, desiccating and antiseptic action. Another advantage is that after desiccation it exerts a slight pressure on the skin. The secretion, inflammation and pain are said to disappear rapidly after its application.

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Hahn, Fortschritte der Medizin 1911, No. 2.

Bruch, Münchener medizinische Wochenschrift 1911, No. 25.

Dreuw, Monatshefte für praktische Dermatologie 1911, No. 3.

**Indol.**

The use of indol as a test for nitrous acid and nitrites was suggested by Bujwid. Dané has recently described a modification of the Bujwid reaction. According to this the reagent consists of a solution of 0.02 gramme of synthetic indol in 150 c. c. of alcohol 95 p. c. If 2 to 5 c. c. of this reagent be added to water containing nitrites and the mixture be acidified with 50 p. c. sulphuric acid, in the course of a minute, according to the amount of nitrous acid present, a pink to red coloration will be produced, the intensity of which makes a colorimetric determination of nitrous acid possible. As this test shows the presence of nitrous acid in a dilution of 1 part in 2,500,000 parts of fluid, it is highly suitable as a test for the acid in vegetable substances and in sulphuric acid.

Indol is also useful as a test for various carbohydrates, e. g., dextrin, mannite, starch, cellulose, gums and glucosides. For this purpose 3 to 4 c. c. of hydrochloric acid are added to the diluted carbohydrate solution (0.5 gramme), this is heated to boiling and 3 to 4 drops of a 0.1 p. c. alcoholic solution of indol are added. According to the amount of carbohydrate present, a pale yellow to orange colour is obtained. The reaction still takes place if a mixture of 1 to 2 drops of a 0.01 p. c. carbohydrate solution with 5 c. c. of water is used. Concentrated carbohydrate solutions, which are coloured when heated with hydrochloric acid alone, should first be sufficiently diluted with water. In the place of indol, carbazol may also be used as a test for the carbohydrates named. For this purpose an alcoholic solution of carbazol, saturated in the cold, is used, of which 1 to 2 drops are mixed with 0.5 c. c. of the carbohydrate solution, and 1 c. c. of pure sulphuric acid is added. At the junction of the carbohydrate solution and the sulphuric acid a violet-red ring is formed, and on mixing a red coloration is produced. This test is less sensitive than the indol test and should always be accompanied by a control test.

**Insipin.**

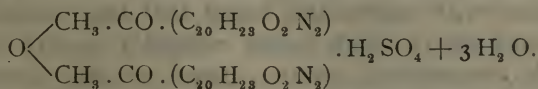
Insipin is the name applied to the sulphate of quinine di-glycol-ester, which is an almost tasteless preparation. It is

Bujwid, Merck's Reagenzien-Verzeichnis 1908, p. 39.

Dané, Bulletin de la société chimique de France (4th Ser.) Vol. 9, p. 354.

Fleig, Journal de pharmacie et de chimie 1908, II, p. 385.

only slightly soluble in hot water or hot alcohol and contains 72.2 p. c. of quinine. Its chemical formula is:



Werner gave it in doses of 0.2 gramme (3 grains) 6 times a day in malaria, and usually, though not always, obtained a prompt action. More frequent administration or the use of larger doses is said to yield a more reliable action, e. g., 0.2 gramme (3 grains) given 9 times a day, or 0.4 gramme (6 grains) given 6 times daily. In the author's opinion, the preparation is more suitable for children than for adults; for children it is said to be particularly suitable when mixed with chocolate.

### Iodine.

In surgery the disinfection of the site of operation by means of iodine is gaining more and more importance. Although it is questioned by some whether tincture of iodine has a strong bactericidal action, yet painting with iodine is recognised to be one of the best, if not the best method for disinfecting the skin. A. Hofmann, E. Casassovici, Mantelli, P. Sick and A. Hofmann, H. Küttner, Champeaux, Lenormant, Bertelsmann, W. Evans, Turner and Catto, C. Decker, Noguchi and K. Fritsch have reported their experiences on this subject.

Casassovici considers tincture of iodine to be an excellent antiseptic in minor surgery. In his experience, infected wounds

Werner, Deutsche medizinische Wochenschrift 1911, p. 2008. —

Medizinische Klinik 1911, p. 1948.

Hofmann, Münchener medizinische Wochenschrift 1911, No. 3.  
Casassovici, Spitalul 1910, No. 17.

Mantelli, Gazzetta degli ospedali e delle cliniche 1910, No. 146.

Sick-Hofmann, Zentralblatt für Chirurgie 1911, No. 23.

Küttner, Archiv für klinische Chirurgie 1911, Vol. 95, No. 1.

Champeaux, Journal des praticiens 1911, No. 17.

Lenormant, Presse médicale 1911, 13<sup>th</sup> March.

Bertelsmann, Zentralblatt für Chirurgie 1911, No. 26.

Evans, Lancet 1911, 7<sup>th</sup> January.

Turner-Catto, Lancet 1911, 18<sup>th</sup> March.

Decker, Deutsche medizinische Wochenschrift 1911, No. 23.

Noguchi, Archiv für klinische Chirurgie, Vol. 96, No. 2.

Fritsch, Beiträge zur klinischen Chirurgie 1911, Vol. 75, No. 1.

can be rendered aseptic by its use. He himself painted extremely dirty wounds with iodine, sutured them and again painted them with iodine and found that they healed rapidly. Mantelli used the Grossich iodine method\*) in over 700 operations with unequivocal results. Based on his investigations, he considers tincture of iodine to possess a powerful bactericidal and antiseptic action, whereas Decker, for example, in his bacteriological investigations, was unable to demonstrate any bactericidal action of tincture of iodine. He therefore believes that the action of iodine is due to a lowering in the capacity of the skin for giving off germs. Whether this be the case or not, painting with iodine is an excellent method of disinfection, even for abdominal operations, as is evident from the communications of Sick and Hofmann. In opposition to Proping, who states that after iodine disinfection for abdominal operations the danger of post-operative intestinal obstruction is increased, Hofmann asserts that the iodine method is an ideal procedure; in about 100 laparotomies he had no case of intestinal obstruction. The iodine method is said to be of good service in septic laparotomies, in which adhesions are in any case formed between the intestinal coils. Sick, in 150 operations for appendicitis, had no case of obstruction by adhesions.

Küttner suggested the following technique: On the evening before the operation the patient has a bath, after which the operation area is shaved. On the day of the operation, at the commencement of anæsthesia, the operation area is painted with 5 p.c. tincture of iodine and covered over with a sterile cloth. Immediately before the operation the painting with iodine is repeated. In urgent operations the skin is shaved while dry and twice painted with 5 p.c. tincture of iodine, without any other measures. Over sensitive areas of the skin a single painting suffices. The eczema following the iodine treatment, which has been observed and censured by others may, according to Küttner, be avoided if only a 5 p.c., freshly prepared tincture of iodine is used and no other disinfectants are applied beforehand. Bertelsmann recommends for this purpose that after operation only a thin non-airtight gauze dressing be applied, and no cotton wool.

Excellent though painting with iodine be both for clean and dirty wounds, it is of no use for suppurating wounds,

\*) Compare Merck's Report 1910, p. 219.

especially for abscesses having a pyogenic membrane, for this membrane hinders its deeper action. But after the removal of the pus iodine tincture is of use, for it hastens the healing of the wounds. Besides the application of iodine, Champeaux recommends for wounds soiled with earth or manure a prophylactic treatment with tetanus serum.

Turner and Catto used for iodine disinfection either a 2.5 p.c. tincture of iodine, or a solution of 30 grammes (1 oz) of iodine and 30 grammes (1 oz) of potassium iodide in 500 c.c. (17 oz) of water, which before application was mixed with an equal volume of methyl alcohol\*). The method of application is similar to that described by Küttner, and the authors specially emphasise that the tincture of iodine should only be applied to perfectly dry skin.

Evans used an alcoholic solution of iodine 1 in 80 and believes that a single application is sufficient in the majority of cases.

According to Fritsch, the disinfection of the site of operation with 5 p.c. tincture of iodine is the method of choice. Even though its bactericidal action be slight, it develops great powers of penetration and fixation and the results are equal or superior to those obtained with other methods. At the same time the procedure spares the patient and is quickly performed.

With regard to the treatment of wounds with tincture of iodine, reference may be made to the communication by Payr. Further, it may be noted that A. Talassano claims to have had most encouraging results from the use of a 2 p.c. alcoholic solution of iodine in burns of the second and third degree.

Should the brown discoloration of the skin caused by disinfection with iodine be regarded as a troublesome feature of the method, advantage may be taken of a suggestion advanced by F. Snoy. The author removed the iodine from the skin and the clothing by the employment of a warmed, concentrated solution of sodium thiosulphate (sodii hyposul-

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\*) Alcohol might be used for the same purpose. The employment of methyl alcohol is not advisable. Compare the article on "Methyl Alcohol" in this Report.

Payr, Münchener medizinische Wochenschrift 1911, No. 35.

Talassano, Semaine médicale 1911, p. 454.

Snoy, Deutsche medizinische Wochenschrift 1911, No. 4.

phis), which converts the iodine into colourless salts, which are soluble in water and can therefore be easily washed off (sodium iodide and sodium tetrathionate). This procedure is without disadvantage either to the skin or to the clothing.

W. Gilbert speaks in favour of the treatment of *ulcus corneae serpens* with concentrated tincture of iodine, which may be prepared by evaporating ordinary tincture of iodine to one third of its original volume. With this the edge of the ulcer is touched daily until it assumes an intense brown colour. If the advance of the process is not immediately inhibited and the edge of the ulcer breaks down, further treatment with iodine is not permissible.

Tincture of iodine has also been recommended for external use by Schmid for disinfection in operative midwifery, by F. Franke before and after operations for surgical tuberculosis, by Babes, Ferrari and Mario for erysipelas, by O. Hildebrand in the form of injections for gonorrhœal joint affections, and for internal use by Uftugéaninoff for exanthematous typhoid. Its last-named use may prove of interest in view of the author's excellent results. He gave 3 to 4 drops of tincture of iodine in 30 c. c. (1 oz) of red wine 3 to 4 times a day, a mixture which was always readily taken and did not give rise to iodism. Its favourable influence on the temperature and the exanthema was unmistakable.

As regards the solution of iodine in benzine recommended by Heussner, it will be remembered that objection was taken to the corrosive action of this solution\*). According to communications by E. Levy and A. Hörrmann, this troublesome by-effect of iodine-benzine, which in other respects is so valuable, is due not to any corrosive property of iodine, but to the benzine. By careful handling of the

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Gilbert, *Fortschritte der Medizin* 1911, p. 265.

Schmid, *Zentralblatt für Gynäkologie* 1911, No. 25.

Franke, *Zentralblatt für Chirurgie* 1911, No. 28.

Babes, *Buia, Spitalul*, 1911, No. 17.

Ferrari, *Gazzetta degli ospedali e delle cliniche* 1911, No. 37.

Mario, *Revue internationale de médecine* 1911, p. 330.

Hildebrand, *Berliner klinische Wochenschrift* 1911, No. 31.

Uftugéaninoff, *Berliner klinische Wochenschrift* 1911, No. 42.

\*) Compare Merck's Report 1910, p. 221.

Levy, *Münchener medizinische Wochenschrift* 1911, p. 302.

Hörrmann, *Münchener medizinische Wochenschrift* 1911, p. 1130.

iodine-benzine solution, however, a corrosive action on the skin is said to be avoided with certainty and without difficulty.

### **Iodipin.**

Injections of iodipin are among the most effective measures in the treatment of syphilis, as is shown by the numerous communications\*) regarding this important antisyphilitic, which have previously been referred to here. This fact has found further confirmation in the publications of F. Filarétopoulos, S. Hirsch and C. H. A. Westhoff. Hirsch, with regard to the communications of Buss\*\*), refers to the old experience that by means of a few injections of iodipin a large amount of iodine can without harm be introduced into the system, which is otherwise only possible by the prolonged internal administration of iodine preparations. The author also again emphasises the chief feature of iodipin treatment, namely the regular, uniform action of iodine on the diseased organism. The results obtained by him with iodipin show up the value of the drug in the best light. Filarétopoulos also speaks of iodipin in an appreciative manner. In a case of tertiary arthritis, in which treatment with mercury and iodine had failed, 12 injections of iodipin caused the swelling of the knee to disappear, whereupon the patient was able to walk. He obtained an equal success in paresis of the lower extremities with symptoms of spinal paralysis. He also records favourable results in cases of multiple cutaneous gummata, syphilitic hemiplegia and tabes.

In the experience of these authors, the technique is simple; in order to avoid pain care must be taken that both iodipin and syringe are sufficiently warmed before the injection, that the cannula used has not too narrow a bore, so that not too much force is required for the injection, and that the injection is made as slowly as possible into the gluteal or interscapular region, by which means induration at the site of injection may be avoided. No noteworthy disadvantages have ever been observed as a result of this procedure.

\*) Merck's Reports 1897—1910.

Filarétopoulos, *Journal médicale de Bruxelles* 1911, No. 30.

Hirsch, *Deutsche Medizinische Zeitung* 1911, No. 24.

Westhoff, *Wochenschrift für Therapie des Auges* 1911, No. 32, Vol. 14.

\*\*) Buss, Merck's Report 1910, p. 224.

In a case of Menière's disease, following upon specific disease of the labyrinth and accompanied by deafness and vertigo, Hirsch gave an injection of 10 c.c. ( $\frac{1}{3}$  oz) of iodipin on alternate days. The subjective troubles diminished after the first week and almost disappeared after 20 injections. The repetition of the treatment in a few months led to permanent cure. In another case of chronic nephritis with severe dyspnoea the patient, besides digalen, was given an injection twice a week of 10 c.c. ( $\frac{1}{3}$  oz) of iodipin below the scapular region. The patient, who was previously barely able to move, had so far recovered in 8 weeks that he was able to resume his occupation. The existing arterio-sclerosis was also favourably influenced by the treatment.

Very good results obtained by iodipin are reported by Westhoff. In a case of chronic iridocyclitis, which had resisted all treatment, even with salvarsan, the author tried some injections of 25 p.c. iodipin (10 c.c. [ $\frac{1}{3}$  oz] each). "Strange to say, the ciliary injection disappeared almost totally and the hypotonia improved, so that now the bulb can again be felt. In this case salvarsan had no action while the old and tried iodine, given subcutaneously, worked wonders." Iodipin also proved useful in a case of iritis syphilitica, which had previously been treated with mercury and salvarsan without success. After the subcutaneous injection of 6, 8, and 10 c.c. of iodipin (25 p.c.) the eye improved considerably. The redness disappeared and the vision became normal.

A few authors, such as Warfield and Gorbатов, have recently suggested that, in order to facilitate the injection of iodipin, smaller doses (1 to 3 c.c.) should be given, and the injections repeated more frequently.

A. Daiber reported on the value of iodipin in infective diseases. The author showed that iodipin was very useful in the treatment of these diseases, as the drug appears to promote and assists in the immunisation processes. In 10 out of 12 cases of scarlet fever he was able to confirm that injections of iodipin improved the condition of the patients and exerted a favourable influence on the disease. Two to three days after the injection of a sufficient amount none of the cases which were running a favourable course showed

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Warfield, Merck's Archives 1911, No. 2.

Gorbатов, Wratschebnaja Gaceta 1911, No. 41.

Daiber, Medizinische Klinik 1911, No. 10.

a rise of temperature worthy of mention. The general condition was always markedly improved, usually on the second day after the injection. In 2 fatal cases no action analogous to that in the other 10 cases could be expected. In epidemics of scarlet fever the author advises that the patients should receive injections as early as possible and before the eruption of the rash, as in some cases the disease was thereby aborted. The dose, according to the age of the child, is 5 to 10 grammes ( $\frac{1}{6}$ — $\frac{1}{3}$  oz) of iodipin (25 p.c.). According to Dai-ber, there is a prospect of iodipin acting as a symptomatic in scarlet fever, and possibly also in variola.

Moreover C. M. Mercurios used iodipin injections for cerebro-spinal meningitis with so much success that further tests in suitable cases would appear both desirable and justifiable. The case described by the author was that of a patient aged 18 suffering from very protracted meningitis, which did not react to repeated injections of serum. The injections of iodipin tried as an experiment led to the surprising result that the temperature fell within 48 hours and the remaining symptoms gradually disappeared. During convalescence the author also administered iodipin internally in the form of tablets.

The antipyretic action of iodipin is also confirmed by Kramer, who used the drug in febrile affections during the puerperium. He injected 10 c.c. ( $\frac{1}{3}$  oz) of iodipin (10 p.c.) on 5 consecutive days, whereupon there was a marked fall in the temperature. On the return of the fever, after leaving off the drug, he repeated the injections as required. The general condition is said to be specially improved by iodipin.

A communication by A. Gorbato w as to the value of iodipin in diseases of the heart and arteries is also of interest. In a large number of cases (arterio-sclerosis, angina pectoris, stenocardia, myocarditis and aneurysm) the author was able to confirm the definite influence exerted by iodipin. He emphasises the improvement in the general condition, the regulation of the bowels in constipated individuals, the favourable influence on sleep and the alleviation or total absence of the painful attacks. In 2 cases of aneurysm and dilated aorta, the examination by Röntgen rays after 2 injections of

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Mercurios, *Grèce Médicale* 1911, No. 15—16.

Kramer, *Münchener medizinische Wochenschrift* 1911, p. 1160.

iodipin showed a diminution of the aneurysm, or of the circumference of the aorta.

S. Goldflam, in 2 cases in which large doses of iodipin (25 p. c.) were being given, i. e., 186 and 400 grammes respectively within a few weeks, observed symptoms of iodism resembling those of Graves' disease, and therefore advises that large doses should only be given with the greatest caution to patients suffering from Graves' disease, goitre and arteriosclerosis, as well as in a variety of other diseases.

J. Zilz gave iodipin in actinomycosis as a supplementary treatment after operation. The patient was given 30 drops of iodipin (25 p. c.) 4 times a day in milk, a form in which it was well taken and caused no troublesome effects. Should the oily taste of iodipin render its administration difficult, the preparation may be given in the form of the well known iodipin tablets.

As in Röntgen ray examinations peculiar shadows had been observed in those parts into which iodipin had been injected, which had led to the belief that the iodipin gave rise to a species of calcification, Fritsch made experiments which showed that weeks and months after the intramuscular injection of iodipin these shadows could be recognised, and were proved to be due to unaltered iodipin. The excised tissue showed no damage either microscopically or macroscopically. The opacity of iodipin to X rays may thus be of diagnostic use, especially for the demonstration of cavities and fistulæ. The author's investigations also confirmed the well known fact that iodipin is deposited unaltered and is slowly absorbed.

### **Iodipin For Veterinary Use\*).**

J. Loidolt gave iodipin (25 p. c.) together with potassium iodide subcutaneously for a prolonged period for moon-blindness in horses and came to the conclusion that these iodine preparations aid and hasten the absorption of

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Goldflam, Berliner klinische Wochenschrift 1911, p. 423.

Zilz, Oesterreichisch-ungarische Vierteljahresschrift für Zahnheilkunde 1910, Vol. 26, No. 4.

Fritsch, Beiträge zur klinischen Chirurgie, Vol. 75, No. 1.

\*) Compare Merck's Reports 1905—1910.

Loidolt, Oesterreichische Wochenschrift für Tierheilkunde 1911, p. 2.

the products of internal inflammation of the eyes. Sustmann prescribed iodipin with apparent success for lymphatic constitution, pneumonia and its consequences. He injected the drug (10 and 25 p.c.) subcutaneously. It displayed a uniform iodine action, lasting for months.

### Iodival.

In all diseases in which internal iodine medication is required, e. g., syphilis, tuberculous adenitis, scrofula, asthma, arterio-sclerosis, etc., iodival\*) has, according to the communications of E. Hesse, B. J. Wiljamowski, Bayer, C. Brexendorff, Pohlmann and O. Westphal, proved efficient.

According to Hesse, tertiary syphilitic cutaneous affections form the principal field of usefulness for iodine. The majority of the 22 cases treated by him with iodival reacted promptly to the drug, while only in a few cases was the reaction slow. In a severe case of malignant syphilis, however, it failed to take effect, even on increasing the dose to 6 tablets a day. With the exception of this case, the author observed the disappearance of the ulcers in every case of syphilitic ulceration; but in a few cases of gummatous ulceration the ulcers cleared up slowly when suitable local treatment was carried out simultaneously. In these cases the author hopes for better results after previous treatment with salvarsan. Pohlmann also considers iodival an excellent remedy for use together with salvarsan and mercury; it is better borne than potassium iodide.

Westphal obtained satisfactory results by the use of iodival in asthma due to extreme obesity, in bronchitis and especially in arterio-sclerosis accompanied by attacks of vertigo. The drug acted well in a case of stenocardia with commencing arterio-sclerosis, in which the author administered one iodival tablet 3 times a day. Double this dose caused coryza, which,

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Sustmann, Berliner tierärztliche Wochenschrift 1911, p. 610.

\*) Compare Merck's Reports 1908—1910.

Hesse, Deutsche medizinische Wochenschrift 1911, p. 444.

Wiljamowski, Praktischeski Wratsch 1911, No. 5.

Bayer, Therapie der Gegenwart 1911, No. 7. — Wiener medizinische Zeitung 1911, No. 35.

Brexendorff, Fortschritte der Medizin 1911, No. 30.

Pohlmann, Berliner klinische Wochenschrift 1911, No. 43.

Westphal, Medico 1911, No. 43.

however, soon disappeared on reducing the dose to 3 tablets a day. No gastric disturbance was observed. Iodival also proved of service in scrofula in children. It caused the rapid disappearance of eczema and adenitis, and was well borne. For tuberculous adenitis Bayer recommends the use of Koch's old tuberculin together with iodival, as the therapeutic effect is good. In cerebral syphilis he gave 0.3 gramme (5 grains) of iodival 3 times a day for 6 weeks, with the result that the pupillary reaction almost returned to normal, the slight ptosis disappeared and the mental condition improved. Only the deafness remained. In 3 cases of emphysema, iodival was very effectual in two, and failed in the third.

### **Iodocitin.**

According to C. Neuberg, this new preparation is a combination of iodine, lecithin and albumin, which is issued in the form of tablets. His investigation proved that each tablet contains 0.0245 gramme of inorganically combined iodine, and 0.0374 gramme of organically combined iodine. Experiments on human beings and animals showed that the iodine introduced into the system in the form of iodocitin was excreted both in the urine and in the fæces. After the administration of 3 tablets (0.173 gramme of iodine), the author found 0.09 gramme in the urine at the end of 24 hours, and 0.043 gramme after another 24 hours. On the third day no further iodine was discovered, so that retention of iodine does not occur. The preparation was borne very well. The chemical analysis of iodocitin by P. Müller led to similar conclusions: he found an average total of 0.06 gramme of iodine in the tablets.

The indications for iodocitin are the same as for the alkaline iodides, viz., arterio-sclerosis, syphilis, etc. Isaac in the beginning gave one tablet 3 times a day with the meals and gradually increased the dose to 8 tablets a day. With this dose he never observed iodism or gastric disturbances. The appetite and general health were improved; and the drug, on account of the lecithin contained in it, is said to have had an excellent effect on syphilitic lesions, especially when following upon treatment with mercury and salvarsan.

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Neuberg, *Therapie der Gegenwart* 1911, p. 359.

Müller, *Zentralblatt für die gesamte Therapie* 1911, p. 395.

Isaac, *Medizinische Klinik* 1911, p. 1541.

### Iodoform.

According to H. Mowat, iodoform is useful in the form of inunction cures for basilar meningitis. For this purpose an ointment is used made of 1 gramme (15 grains) of iodoform and 30 grammes (1 oz) of vaseline, which is rubbed twice a day into the neck and the occiput. Besides this, small internal doses of potassium bromide and potassium iodide are given. In two cases of typical basilar meningitis this treatment, according to the author, brought about rapid improvement and cure.

T. W. Dewar states that he has obtained satisfactory results in phthisis with comparatively small doses of iodoform. He gave intravenous injections of 0.015 to 0.06 gramme ( $\frac{1}{4}$  to 1 grain) in ethereal solution 3 times a week, keeping the patient under careful observation. As soon as the temperature was raised or the expectoration increased, he diminished the dose. In advanced cases he noticed an improvement in the clinical symptoms, and in the course of a year, by dint of care and diet, the progress of the disease even became arrested. The early employment of the treatment described is said to effect a cure in the course of a few months, even without the adoption of special measures. The action of small doses of iodoform may be explained in various ways. Thus it may be due to the bactericidal power of the drug, or to its products of decomposition (iodine and formaldehyde?), or to an increase in the phagocytes brought about by the iodoform, or to the formation of iodoform antitoxin. Dewar refrains from giving a definite opinion. As the author's experiments extend over 10 years, the suggestion of iodoform treatment in phthisis deserves full consideration.

### Iodostarin.

This new organic preparation of iodine is the iodine addition product of taririnic acid, taririnic acid di-iodide, of the chemical formula  $\text{CH}_3 \cdot (\text{CH}_2)_{10} \text{Cl} = \text{Cl} \cdot (\text{CH}_2)_4 \text{COOH}$ , melting at  $49^\circ \text{C}$ . It forms white, shining crystalline scales, which are odourless and tasteless, containing 47.5 p. c. of iodine. It is insoluble in water, slightly soluble in cold alcohol, readily

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Mowat, *Lancet* 1911, I, p. 24.

Dewar, *Glasgow Medical Journal* 1911, p. 7, (July).

soluble in hot alcohol, in ether, chloroform and benzol. Iodostarin itself is not affected by light, not so its solutions, which after short exposure to light turn brown under separation of iodine.

The pharmacological investigations of C. Bachem and E. Herzfeld and M. Haupt show that iodostarin displays only a very slight toxic action in the animal, and in the human system. A fatal dose amounts to about 5 grammes per kilogramme of rabbit. Iodostarin passes through the stomach unaltered and ionised iodine is only split off in the duodenum, and more especially beyond it. After about half an hour the presence of iodine may be demonstrated in the urine and the saliva. About 75 to 80 p. c. of the total iodine ingested as iodostarin is excreted in the urine in the course of 3 days. The elimination of iodine is therefore slower than when potassium iodide is used, in consequence of which the action is more prolonged.

Iodostarin is issued in the form of tablets of 0.25 gramme (4 grains). It is intended for internal medication. Clinical investigations have, as far as I know, not yet been published.

### Iothion.

The absorption of iothion\*) through the skin is, according to Baldoni, considerably hastened if after rubbing in the drug chloroform be applied. Whereas, according to the author's investigation, about 15 to 30 p. c. of iothion is absorbed through the skin, the application of chloroform is said to increase its absorption to 25 or 45 p. c. In suitable cases iothion should therefore be combined with chloroform in order to increase its action. Further, the author's pharmacological investigations showed that after inunction with iothion the strongest iodine reaction was to be found in the kidneys and liver. The presence of iodine can also always be demonstrated in the fat, blood and muscles; while in the brain, though it always contains iodine, only very small amounts are present. He found the stomach, bowel and lungs free from iodine.

Bachem, Münchener medizinische Wochenschrift 1911, p. 2161.  
Herzfeld-Haupt, Medizinische Klinik 1911, p. 1426. — Compare also Herzfeld and Heimann, Medizinische Klinik 1911, p. 1858.

\*) Compare Merck's Reports 1904—1910.

Baldoni, Bollettino della reale accademia medica di Roma, Vol. 36, No. 6.

Hauser reports good results with iothion treatment in tuberculous joint affections. In a series of cases (in swelling at the shoulder, knee, elbow, wrist, etc.) he applied 10 to 25 p.c. iothion, which was always followed by improvement in the inflammatory symptoms, provided the disease had not yet attacked the bones themselves, but had only to a greater or less degree attacked the soft parts. In these cases the author could point to success where other methods of treatment had failed. Further, in 3 cases of ganglion of the wrist, the ganglia definitely disappeared within a few weeks after the application of 10 p.c. iothion and moist compresses; while with very large ganglia and extensive fungus of the tendon sheaths of the hand a cure was only effected by means of operative procedure. Strachnow also obtained good results by using a 10 to 25 p.c. iothion ointment in rheumatic and gouty affections. In acute parametritis and erosions of the cervix, he obtained good results by the application of tampons which had been soaked in 2 p.c. iothion-glycerin.

### **Ipecacuanha.**

The root of ipecacuanha, as is well known, has been recommended by various investigators\*) as a valuable drug in the treatment of amœbic dysentery. As the action of the drug is thought to be due to the ipecacuanhic acid it contains, it has been customary to eliminate the emetic action of the root by extracting the alkaloids and by employing the so-called de-emetised ipecacuanha. But, according to V. Brem and H. Zeiler, ordinary powdered ipecacuanha may be used in pill-form so long as the drug is prevented from dissolving and exerting its action in the stomach. This result is said to be attained by coating the pills with salol; this should not be too thick, as the ipecacuanha pills will then be passed unaltered, nor too thin, or the desired object will not be attained. A layer of salol about 1.5 mm. in thickness is said to be most suitable. In 14 cases of dysentery and amœbic infection the authors obtained results such as could not have been

Hauser, Medizinische Klinik 1911, Nr. 26.

Strachnow, Wiener medizinische Zeitung 1911, No. 16.

\*) Compare Merck's Reports 1891, 1892, 1893, 1896, 1902, 1904.

Brem-Zeiler, American Journal of Medical Sciences 1910, November, p. 669.

obtained by the ordinary methods of treatment by irrigation of the bowel (saline solution, quinine, thymol). According to their instructions the patient must remain in bed, for 6 hours before administering the drug he must take neither milk nor solid food, and for the last 3 hours before he must take nothing whatever. The ipecacuanha pills mentioned above are used, each containing 0.06 gramme (1 grain) of ipecacuanha; on the first day 60 to 80 of these pills are administered, and the dose is reduced by 5 pills a day until the daily dose amounts to 10 pills. Occasionally the goal is quickly reached by giving 40 pills 3 times a day.

To avoid failure and to prevent vomiting, radix ipecacuanhæ de-emetinisata should be used, as the exact amount of salol coating is then of less moment.

### Isopral.

As a preliminary to chloroform anæsthesia, isopral is said by V. E. Mertens to be useful when given in the form of rectal injections. After rectal lavage, the patient is given rectally 0.1 gramme ( $1\frac{1}{2}$  grains) of isopral pro kilogramme of body-weight, in the evening and the morning before the operation, by means of a tube passing 20 cm. (8 in.) up the rectum. The isopral solution used for this purpose is prepared as follows. To every 0.1 gramme of isopral 0.1 gramme of ether is added and the solution is made up with alcohol 50 p.c. to 25 c.c. for children, and to 50 c.c. for adults. Thus, if the patient weighs 55 kilogrammes, 5.5 grammes of isopral and 5.5 grammes of ether and enough alcohol to make up 50 c.c. of fluid are used for the injection. An hour after the isopral injection the chloroform anæsthesia should be begun. The advantages of this method are that the patient goes to sleep after the injection and does not notice the preparations necessary for the operation. The stage of excitement therefore does not occur even in alcoholics. Besides, less chloroform is needed to maintain anæsthesia, the patients do not vomit, usually sleep the whole day, they need not be watched and they are spared the post-operative discomforts of the first day. According to Mertens, the method described is also useful for abdominal operations and does not lead to meteorism. Only in one case, in which it had not

been possible to carry out rectal lavage, proctitis occurred and lasted for 5 days. Otherwise isopral injections are said to be free from danger.

L. Burkhardt used isopral intravenously as an anæsthetic, and found that it possessed several advantages over hedonal. He used a 1.5 p. c. sterile solution of isopral in Ringer's solution, which was injected with aseptic precautions. He injected 40 c.c. per minute. In women the stage of tolerance was reached after the use of 100 to 160 c.c. (1.5 to 2.4 grammes of isopral), in men after the instillation of 130 to 200 c.c. (1.9 to 3.0 grammes of isopral). For anæsthesia lasting 30 to 35 minutes 220 to 300 c.c. were used. In 12 cases the anæsthesia took a normal course, while in only 2 cases was a condition of excitement observed on waking. No other disadvantages of the method were noted. In the presence of cardiac lesions the author does not consider isopral anæsthesia suitable. I have already briefly described the combination of intravenous isopral injection with intravenous ether injection in the article on ether\*).

### Kalmopyrin.

The attempts to replace acetyl-salicylic acid, which is soluble with difficulty in water, by soluble salts of this acid have not as yet been attended with complete success, because the salts of acetyl-salicylic acid, such as the sodium salt, are difficult to prepare and are rapidly saponified in damp air or in aqueous solution, i. e., are decomposed with formation of acetates and salicylates. As acetyl-salicylic acid is not insoluble and dissolves with sufficient rapidity on internal administration and is also absorbed with sufficient rapidity, the only advantage of its salts in therapeutics is that they can be given in aqueous solution alone, or in combination with other soluble drugs. But in aqueous solution sodium acetyl-salicylate is very rapidly decomposed, and lithium acetyl-salicylate is also partially decomposed in a comparatively short time with formation of lithium acetate and lithium salicylate, so that the acid index, according to S. Fränkel, is increased within 3 days from 0.5 to 11 p. c. From this it follows that a solution

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Burkhardt, Münchener medizinische Wochenschrift 1911, No. 15.

\*) Compare p. 231 of this Report.

Fränkel, Süddeutsche Apothekezeitung 1911, p. 621.

of lithium acetyl-salicylate cannot be kept for long and is best prepared immediately before use. Now calcium acetyl-salicylate, kalmopyrin, is said to offer special advantages, as it is neither hygroscopic nor is it decomposed in aqueous solution as rapidly as is the lithium salt. Kalmopyrin is a white powder with a slight chalky taste and is readily soluble in water; in an anhydrous condition it contains 10 p. c. of calcium and 90 p. c. of acetyl-salicylic acid.

The indications for kalmopyrin are the same as for acetyl-salicylic acid. A. Klier prescribed it for polyarthritis, for arthritis uratica with a high degree of neurasthenia, and for the febrile symptoms in tuberculous subjects. In the first two of these it rapidly alleviated the pain, but in tuberculous subjects it caused such severe attacks of perspiration that the author advises against its use in patients with severe tuberculosis. In sciatica its analgesic action was only slight, in periostitis mandibulæ it was scarcely apparent. For rectal use kalmopyrin is said to be better than hydopyrin, as in this case the constipating action of the calcium component also comes into action. Klier administered kalmopyrin in doses of 0.5 to 1 gramme ( $7\frac{1}{2}$ —15 grains), and in daily doses of 3 grammes (45 grains). Even with daily doses of 5 grammes (75 grains) he observed no troublesome secondary effects.

### Lecithin.

Since the valuable therapeutic properties of lecithin have become known, the market has been flooded by a large number of lecithin preparations, which have been prepared from the most varied lecithin-containing raw materials; some of the preparations are free from objection, others are more or less questionable, containing only very little true lecithin or perhaps nothing more than lecithalbumin. But for therapeutic purposes only absolutely pure lecithin should be used if reliable physiological and pharmacological action be desired. According to J. Nerking, the preparation should be free from cholesterin, the action of which is opposed to that of lecithin, and from all fatty acids; for lecithin is a very labile substance and in the presence of free acids decomposes on keeping. Further, it is not a matter of indifference for

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Klier, *Therapie der Gegenwart* 1911, p. 309.

Nerking, *Allgemeine medizinische Zentralzeitung* 1911, p. 631.

the therapeutic value of lecithin whether it be obtained from animal or from vegetable sources, because vegetable lecithin can only with difficulty be purified of its impurities. Nor has lecithalbumin the same action as pure lecithin, as has been recently pointed out by Mendel. Starting from this fact, I have for years endeavoured to prepare an absolutely pure lecithin and my **Lecithin puriss. ex ovo** represents the realisation of this aim. This preparation contains 95 to 97 p. c. of pure lecithin; it gives a perfectly clear solution with alcohol and ether.

The tests and the quantitative estimation of lecithin have been discussed by C. Casanova, Siedler, Sattler and P. Salzmann.

Casanova describes a reaction for the identification of lecithin; an ethereal solution of lecithin is mixed with a 10 p. c. solution of ammonium molybdate and concentrated sulphuric acid is added so as to form a layer below the mixture; at the junction of the fluids a reddish, then green and finally an intense blue coloration is produced. Cholesterin and phytosterin are said not to give this colour reaction. Anyone well versed in the chemistry of molybdenum will look with suspicion upon this reaction even without further tests; the blue coloration at least can never be regarded as characteristic, for all oxidisable substances when acted upon by molybdic acid and sulphuric acid reduce the molybdic acid, thus producing a green or blue coloration. Therefore Casanova's reaction is certainly not specific, although under certain circumstances it may be of value as a preliminary test in the investigation of substances containing lecithin. Nor has Casanova's suggestion remained unchallenged. Siedler justly finds fault with Casanova's instructions for carrying out the test, for an ethereal solution of lecithin will not mix with an aqueous solution of molybdenum and the addition of sulphuric acid causes the ether to boil, which would render the layering test useless. He therefore proposes to emulsify a little lecithin with the solution of molybdenum and then to pour this mixture on to sulphuric acid. But he found that wool fat

Casanova, *Bollettino chimico farmaceutico* 1911, p. 309.

Siedler, *Apotheker-Zeitung* 1911, p. 912.

Sattler, *Apotheker-Zeitung* 1911, p. 930.

Salzmann, *Apotheker-Zeitung* 1911, p. 949.

also gives the blue reaction. He therefore refers to the method of investigation for lecithin given by Moreau, Aufrecht, Riedel, Fendler and Virchow. Sattler recommends Thierfelder's method\*), and Salzmann the method of Glikin\*\*). Interesting communications on the estimation of lecithin in raw material and in food-stuffs have been furnished by R. Cohn.

The physiology and pharmacology of lecithin have been discussed by Usuki, Masing, L. Böker, E. Durlach, W. Heubner, H. Stadler and H. Ulrich. The original publications should be consulted, as they do not lend themselves to short abstracts.

Two communications by Voet and Schottin are of therapeutic interest. Voet has found lecithin useful in gastrointestinal auto-intoxication. By the administration of lecithin in conjunction with a diet rich in carbohydrates, together with irrigation of the intestine and hydropathic measures, the author observed a diminution in the toxic symptoms and in the fetidness of the stools, and the disappearance of the paired ethyl sulphates from the urine. These symptoms, according to Voet, appear in the presence of hepatic insufficiency, for the liver supplies the de-toxicating substances in auto-intoxications. Lecithin, according to Schottin, also appears to be of value in migraine. The author has at any rate confirmed this both theoretically and practically.

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Moreau, Bulletin des sciences pharmacologiques 1902, No. 7.  
Aufrecht, Pharmazeutische Zeitung 1903, No. 1.

Riedel, Berichte 1905 and 1907.

Fendler, Apotheker-Zeitung 1905, No. 3.

Virchow, Chemiker-Zeitung 1911, No. 100.

\*) Compare Hoppe-Seyler's Handbuch der physiologischen und pathologischen chemischen Analyse (revised by H. Thierfelder) 1903. 7th Edition.

\*\*) Compare Pflügers Archiv für Physiologie, Vol. 95, p. 107.

Cohn, Zeitschrift für öffentliche Chemie 1911, p. 203.

Usuki, Archiv für experimentelle Pathologie, Vol. 63, p. 270.

Masing, Archiv für experimentelle Pathologie, Vol. 66, p. 71.

Heubner (Böker, Durlach, Stadler, Ulrich), Münchener medizinische Wochenschrift 1911, p. 2543.

Voet, Scalpel 1911, p. 2543.

Schottin, Medizinische Klinik 1911, No. 9. -- Münchener medizinische Wochenschrift 1911, p. 1157.

**Lecithin Preparations Merck.**

In order to render lecithin puriss. ex ovo\*) accessible for therapeutic use and at the same time to exhibit it in an inviting form, I have decided to issue the following preparations of lecithin:

For internal use:

**Lecithin Chocolate** (lecithin. granulatum) is a 10 p.c. granulated mixture of lecithin puriss. with cocoa and sugar, having a pleasant aromatic taste. It is specially suitable for prolonged use and for use in hospitals. One teaspoonful corresponds to about 0.25 gramme (4 grains) of lecithin puriss.

**Lecithin Chocolate Tablets.** (0.25 gramme [4 grains] of lecithin puriss. in each.)

On account of their pleasant taste, and as the peculiar oily taste of pure lecithin is masked as completely as possible, these Lecithin Chocolate Tablets offer a convenient form of administering this preparation, and are readily taken even by sensitive patients.

**Lecithin Cocoa Tablets** (0.25 gramme [4 grains] of lecithin puriss. in each). These tablets are prepared without sugar and are specially recommended for the administration of lecithin in diabetes.

For subcutaneous injection:

**Lecithin emulsion** in normal saline solution is a sterile preparation containing 10 p.c. of lecithin puriss., which is issued in ampoules containing 2 and 5 c.c. This emulsion, prepared in a special manner, contains the lecithin in very fine, uniform suspension and is distinguished by its keeping properties.

These preparations may be used in all indications for lecithin, e. g., in weakly persons or those either bodily or mentally backward, for athrepsia, rickets, scrofula, anæmia, chlorosis, pulmonary tuberculosis, diabetes, phosphaturia, diseases of the spinal cord, osteomalacia, debility following infective diseases, senile debility and nervous diseases such as neurasthenia, hysteria, and further in psychoses, paralysis and tabes.

\*) Compare the preceding article on Lecithin.

Internally, lecithin is given, according to the age of the patient, in doses of 0.75 to 1 gramme (12—15 grains) a day. Thus 3 to 4 teaspoonfuls of lecithin chocolate, or 3 to 4 of the tablets mentioned above, are given daily. Children are given 2 tablets, or 1 teaspoonful of lecithin chocolate twice a day.

For subcutaneous or intramuscular injection 2 c.c. of lecithin emulsion are given to children, and 5 c.c. to adults, especially for mental disorders, impaired digestion and debility.

J. Nerking obtained very good results with the preparations mentioned above in anæmia, chlorosis, neurasthenia, tabes, etc. He considers lecithin puriss. Merck and the preparations made with it to be the best and purest lecithin obtainable at present.

### Lenicet.

As is well known, objections have been raised by several authors against the use of blenolenicet ointments for ophthalmia neonatorum\*). But these, as is evident from the communications of F. Schoeler and Wolffberg, have reference, not to the value of the lenicet ointments themselves, but only to the method recommended by Adam of using these ointments. Schoeler's method differs considerably from that proposed by Adam. As the author considers the cleansing of the eyes to be a point of special importance, and as this cannot well be carried out when the ointment is continuously applied, he prescribes during the day the old method of compresses with or without ice, irrigation with antiseptic solutions, such as solutions of chlorine or potassium permanganate, 2 instillations of a 5 p.c. argyrol solution and painting with a 2 p.c. silver nitrate solution followed by irrigation with saline solution and water. For the night he prescribes the use of a 5 p.c. blenolenicet ointment, to be rubbed into the conjunctival sac. This prevents the severe maceration of the skin of the eye-lids, which is often caused in children by the continuous application of compresses. By this method

Nerking, Allgemeine medizinische Zentralzeitung 1911, No. 46.

\*) Compare Merck's Report 1910.

Schoeler, Münchener medizinische Wochenschrift 1911, p. 1139.

Wolffberg, Münchener medizinische Wochenschrift 1911, p. 1514.

Adam, Merck's Report 1907, p. 159.

of using the ointment its action of diminishing secretion is plainly shown. This fact is also confirmed by Wolffberg.

### Lenigallol.

For the treatment of varicose eczema of the leg, which is well known to be a most resistant form of eczema, a combination of lenigallol and silver nitrate is, according to Wehner, of good service. The procedure is as follows:

All the moist regions of the eczema are dabbed with plugs of cotton wool soaked in a 5 p.c. solution of silver nitrate until they appear dry. In doing this some pressure must be exerted. When the eczematous surface is dry, which may take some minutes, a little piece of gauze covered with a layer of 5 p.c. lenigallol-zinc paste is applied and fixed with a bandage. After 3 days the secretion usually ceases, but should this not be the case an interval of 1 to 2 days is allowed to elapse and the lenigallol treatment is then repeated. This treatment should not take place on more than 3 consecutive days, but may be repeated as often as desired, provided the intervals mentioned above be allowed. In the interim the author recommends the employment of zinc paste or zinc oil. The action of the silver-lenigallol treatment is due to the formation of a thin coating of silver albuminate, which on reduction by lenigallol becomes dry and firm and hastens the healing of the eczema. Lenigallol also relieves itching, an action specially marked in the method mentioned above. In eczema of the genitals and in secondary eczema, lenigallol is also useful. G. Hahn attaches special importance to cleanliness and recommends, besides the treatment of the fundamental disease, the following ointment:

Rp. Lenigallol.	1.0—2.5 grammes (15—40 grains)
Zinc. oxid.	2.0 grammes (30 grains)
Amyl.	2.0 grammes (30 grains)
Ung. aq. rosæ	
Ung. simpl.	aa 50.0 grammes (1 $\frac{2}{3}$ oz)

### Leucofermantin.

In a paper read by E. Müller, the author described in detail the theoretical and practical aspects of antiferment

Wehner, Therapie der Gegenwart 1911, No. 9.

Hahn, Fortschritte der Medizin 1910, No. 45.

Müller, Wiener medizinische Zeitung 1911, No. 40—42.

therapy and pointed out that this treatment offers special promise of success in circumscribed suppuration with a definite margin. In these cases the healing which follows the employment of antiferment is quite different and healthier in character. With a fall in the temperature and the rapid disappearance of œdema, the commencing softening is rapidly brought to a standstill, and by the formation of fresh, healthy granulations the tissue necrosis is very soon sharply limited\*). Even though it must be admitted that the success of antiferment treatment is most marked in those forms of suppuration which lead to abscess formation and which therefore present the best conditions for surgical treatment, yet the above mentioned treatment has a double advantage. The healing process is considerably shortened, the change of dressing is painless, and the cosmetic result in cases requiring surgical treatment is usually better, as only small incisions or punctures are necessary. In certain cases antiferment treatment is even more advantageous than incision.

According to Müller, the indications for leucofermantin are not limited to the special spheres of surgery, gynæcology and ophthalmology, but may under certain conditions be extended to cases of epidemic meningitis, intracranial abscesses, suppurative pleurisy and peritonitis, suppurative diseases of the lung and ulcerative conditions of the gastro-intestinal tract.

W. Hannes expresses a favourable opinion of the value of leucofermantin after radical abdominal operations. He used it together with drainage and found that the secretion rapidly dried up under the influence of the drug and the wound quickly closed by granulation. The women upon whom he operated were on an average discharged with completely healed abdominal wounds not later than 4 weeks after the operation. Leucofermantin is also of good service in leucorrhœa. S. Stocker describes a very simple technique for its application. In catarrh of the cervix, the portio is fixed and cleansed, after which a strip of gauze soaked in leucofermantin is introduced into the cervix and is renewed the following day. After 2 to 3 applications the author usually noticed an improvement. The secretion became slimy and scanty and often

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\*) Compare Merck's Reports 1908—1910 and von Boltenstern, Deutsche Ärzte-Zeitung 1911, No. 11. Hannes, Zentralblatt für Gynäkologie 1911 No. 7. Stocker, Gynäcologia Helvetica 1911, Vol. 11, p. 162.

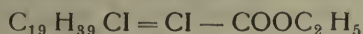
disappeared entirely. If the uterus were enlarged, e. g., if the mucous membrane of the fundus were also involved, 1 to 2 c.c. of leucofermantin were introduced into the fundus under slight pressure by means of a Braun's syringe. In *virgines intactæ* the author merely syringed the preparation into the vagina and left the patient for 10 to 15 minutes in a recumbent position. The results of this treatment were highly satisfactory, indeed quite surprising in those cases which had previously been unsuccessfully treated by means of irrigation. If the discharge recurred after the menstrual period in anæmic individuals, it could be cured by 1 to 2 injections of leucofermantin. On account of the simplicity of its application, Stocker considers it specially worthy of recommendation, because it is more beneficial than treatment with ether.

L. Uthy indicates a method of treating acute and chronic otitis, in which leucofermantin also plays an important part. In acute otitis, after the performance of paracentesis and after cleansing the auditory canal and the tympanic membrane, he swabbed the latter and the perforations with cotton wool soaked in horse serum, and then plugged the auditory canal with cotton wool. If after 3 to 4 days of treatment there was increased hyperæmia coupled with heightened painfulness of the tympanic membrane, the latter and the perforations were dabbed with leucofermantin and a sterile strip of gauze was introduced. He treated chronic otitis with leucofermantin in the same way, after cauterising or removing the granulations and applying horse serum. J. Seligmann was able to confirm the rapid and permanent curative effect of this treatment.

As regards the value of the treatment of abscesses with antiferment, reference may be made to the communications of V. L. Neumayer, H. Boit and H. Ch. Greve.

### Lipojodin.

Lipojodin, di-iodo-brassidinic acid ethyl ester, of the chemical formula:



Uthy-Seligmann, *Monatsschrift für Ohrenheilkunde und Laryngologie* 1911, No. 9.

Neumayer, *Therapeutische Monatshefte* 1911, No. 9.

Boit, *Medizinische Klinik* 1911, No. 16.

Greve, *Ergebnisse der gesamten Zahnheilkunde*, Vol. 1, No. 4, p. 1123.

forms fine, white needles, melting at  $37^{\circ}\text{C}$ ., readily soluble in alcohol, ether, chloroform and fatty oils, but insoluble in water. In a solid state it is stable in diffused daylight; in a liquid state it is gradually decomposed with separation of iodine. Lipojodin contains 41 p.c. of iodine.

According to O. Loeb and R. van den Velden, lipojodin is slowly absorbed if taken with or after the midday meal, and only a small fraction is excreted in the fæces. It is a substance with very pronounced polytropic characters, especially neurotropic and lipotropic; it readily breaks down in fatty and nervous tissue and rather slowly separates iodine ions, thus giving rise to a uniform iodine action. The authors administered the preparation in the form of tablets, in doses of 0.3 to 1.5 grammes (5–24 grains), and daily doses up to 5 grammes (75 grains), which are said to give rise to no unpleasant secondary effects. The indications of lipojodin are the same as for the alkaline iodides.

H. Boruttau, in carrying out confirmatory tests with lipojodin, found that the regularity and uniformity of the physiological behaviour of this preparation were less perfect than might be inferred from the statements of the authors mentioned above. The important question as to whether the lipotropic, neurotropic and polytropic characters of lipojodin constitute a real advantage over other preparations of iodine can only, in his opinion, be decided by extensive clinical investigations.

### **Magnesium-Perhydrol.**

In his trials of treating follicular enteritis by means of magnesium-perhydrol, E. von Olfers' results were so satisfactory that his method may be recommended for further trial in suitable cases. In a series of cases in which an examination of the fæces showed a luxuriant growth of bacillus coli communis, the author attributed the diarrhoea and the cholangitis to the pathogenic properties of these bacteria, and he therefore administered magnesium-perhydrol as an intestinal antiseptic. The patients were given 0.5 gramme ( $7\frac{1}{2}$  grains) 3 times a day after meals, together with a suit-

Loeb-Velden, *Therapeutische Monatshefte* 1911, No. 4.

Boruttau, *Deutsche medizinische Wochenschrift* 1911, No. 43.

von Olfers, *Therapeutische Monatsberichte* 1911, No. 10.

able diet. In every case the author achieved a cure in 3 days by means of this medication.

Magnesium-perhydrol also proved useful in a case of cystitis which had lasted 4 months and was due to the presence of bacillus coli. According to Landenberger, it was cured in 10 days by the administration of magnesium-perhydrol.

Stoessner reports a case of pyloric stenosis and dilated stomach, in which the patient suffered much from flatulence and constipation. The constipation alone was somewhat relieved by enemata, but the unbearable gastric symptoms remained uninfluenced and were only alleviated by the use of narcotics, which again increased the constipation. As the patient could only take porridge and vomited other nourishment, he had become so debilitated that lavage of the stomach was not to be thought of. The use of magnesium-perhydrol in this case gave an excellent result. It was first given in the form of tablets (2 tablets of 0.5 gramme [ $7\frac{1}{2}$  grains] twice a day), later as powder (1 gramme =  $\frac{1}{2}$  teaspoonful twice a day) about half an hour after meals. At first severe attacks still occurred, especially at night, but gradually they decreased in frequency and finally disappeared completely. The bowels were also opened regularly. During a relapse, which occurred later, magnesium-perhydrol had the same favourable effect.

While Stürmer obtained good results by the use of magnesium-perhydrol in diabetes mellitus, M. Hirose states that the drug offers no advantages in the treatment of this disease. F. Daxenberger, on the other hand, used the preparation successfully. He gave a teaspoonful of a mixture of equal parts of magnesium-perhydrol and lime-casein (kalk-kasein) in milk 3 times a day for 4 to 6 weeks in diabetes: in one case he was thus able to reduce the sugar in the urine from 6 p. c. to 1 p. c. and in other cases from 4 p. c. to 1 p. c., or from 3 p. c. to 0.2 p. c. In every case the excretion of sugar was influenced, but the author lays stress on the fact that these favourable results were only obtained by the employment of the com-

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Landenberger, Communicated by the author.

Stössner, Therapie der Gegenwart 1911, No. 7.

Stürmer, Merck's Report 1910.

Hirose, Deutsche medizinische Wochenschrift 1911, No. 36.

Daxenberger, Medico 1911, No. 6.

bination named and not by the administration of either magnesium-perhydrol or of lime-casein alone. Strict diet was not considered necessary as a rule, but a moderate reduction in the carbohydrates was prescribed. The action was always first made manifest by a diminution in the glycosuria, a reduction in the amount of urine and lowering of its specific gravity. The urine soon became neutral or faintly alkaline, the thirst disappeared and also usually any acetone which was present in the urine; there was an improvement in the general health, the nutrition and the strength of the patient, itching of the skin and the digestive disturbances were quickly cured. The only auxiliaries to this treatment were warm baths and rubbing with oil.

For the treatment of acidosis Lenné warmly recommends the frequent administration of a mixture of magnesium-perhydrol, sodium bicarbonate and calcium carbonate (2:1:1).

Winternitz prescribed magnesium-perhydrol with good results, sometimes before and sometimes after food, in the various forms of hyperacidity, especially in the atonic form accompanied by disturbances of motility. He fixed the single dose at 0.5 to 2 grammes ( $7\frac{1}{2}$ —30 grains), and the daily dose at 1.5 to 6 grammes (24—90 grains).

### Magnesium Sulphate.

The antispasmodic and analgetic action of magnesium sulphate in tetanus and tabes and in painful inflammatory conditions is well known: a 25 p.c. aqueous solution of the preparation has been given intraspinally and subcutaneously in these cases. It has also been found that the salt acts as an analgesic when applied locally. This method, which was suggested by Tucker, was successfully carried out by N. H. Choksy in erysipelas and cellulitis. According to the author's instructions, a 15-fold layer of gauze soaked in a saturated aqueous solution of magnesium sulphate is applied to the diseased region and its vicinity, and is covered with waterproof material. The gauze is moistened every 2 hours in order that it may keep wet. As a result of these compresses the swellings, the pain and the temperature are reduced; occasionally there is a loss of sensation, and the occur-

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Lenné, Medizinische Klinik 1911, p. 1309.

Winternitz, Deutsche medizinische Wochenschrift 1911, p. 1391.

Choksy, Lancet 1911, I, p. 300.

rence of a pricking sensation in the hands and arms. The treatment proved most successful in erysipelas of the head.

A. B. Jackson found intramuscular injections of magnesium sulphate very useful in severe cases of acute articular rheumatism in which treatment with salicylic acid had failed. He usually injected 4 c.c. of a 25 p.c. solution into the gluteal region. The injections are said to cause no pain and no secondary symptoms, they are followed by a fall in the temperature and in the pulse rate, and by an improvement in the arthritic symptoms, and lead to a cure in a comparatively short time.

Guthrie and Ryan, based on pharmacological experiments, deny the anæsthetising action of magnesium sulphate. They only attribute to the salt the property of causing muscular paralysis, which may lead to paralysis of the respiratory muscles with consequent partial asphyxia. They state that the presence of anæsthesia depends upon the degree of this asphyxia and should not be regarded as a specific action of magnesium sulphate.

#### Male Fern, Liquid Extract of

The secondary effects of extract of male fern observed by various authors in the last 10 years, led to the inclusion in the German Pharmacopœia, fifth edition, of a maximum dose for this extract (10 grammes pro dosi et die). Filicic acid is usually held responsible for the secondary effects of the extract, although this has not been definitely proved; and the suggestions for the avoidance of filix poisoning hitherto brought forward refer to this. To these belongs the warning against the simultaneous use of castor oil, as this dissolves the filicic acid, which is insoluble in aqueous fluids, so that it can be absorbed. Although the value of this suggestion has been challenged, Drenkhahn has recently further required that during the treatment for tapeworm, fats and fatty foods should be altogether eschewed. The gastro-intestinal tract must also be kept free from alkalis. The author condemns fasting before the cure, and likewise the previous partaking of herrings with onions. If consti-

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Jackson, *Klinisch-therapeutische Wochenschrift* 1911, p. 1116.

Guthrie-Ryan, *Journal of Physiology* 1910, Vol. 26, 1<sup>st</sup> August.

Drenkhahn, *Münchener medizinische Wochenschrift* 1911, p. 2020 and 2796.

pation be present, he gives a mild aperient, such as alder-bark tea or rhubarb powder (but never castor oil or Seidlitz powder), and orders tasty food free from fat, the evening before treatment fresh or preserved raspberries and the next morning, after a cup of sweetened black coffee, 3 grammes (50 min.) of male fern extract (best given in capsules) in sweetened lemon-juice every 10 minutes. As a full dose to be taken within an hour, the author suggests 18 to 20 grammes (300—330 min.) for an adult. If no spontaneous action of the bowels occurs in the course of an hour, the patient is given 0.6 gramme (9 grains) of calomel. With regard to exceeding the maximum dose given in the German Pharmacopœia, the author says: "My method might be disapproved, as it would appear that the fixation of a maximum dose of 10.0 grammes eliminates the danger of poisoning by extract of male fern. But severe symptoms of poisoning have been observed in adults after doses of only 4 grammes, so that the danger is due not to the dose, but to other circumstances attending the cure." Therefore the author recommends that his instructions be followed even with small doses, and that after the cure the ingestion of fats and alkalis be forbidden. It is quite possible that the case of poisoning after 8 grammes of extract of male fern and 16 grammes of castor oil, reported by A. Magnus-Levy, was due to the castor oil. The symptoms of poisoning consisted in a marked increase in the intermittent lameness of a man aged 38, which was accompanied by severe paresis of the muscles of the leg. The condition improved after treatment with iodine, but the author considers complete recovery unlikely. He explains the case as follows: Besides the direct action of the poison on the arterial walls, which are already diseased, and on the cells of the spinal cord, the question arises as to the direct action of the filix poison upon the smooth musculature of the vessels. The arterial spasm attacked the vasa vasorum of the diseased vessels of the leg and those of the lowest part of the spinal cord most severely, and there caused lasting damage.

M. Henius considers that a dose of 18 to 20 grammes

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Magnus-Levy, *Berliner klinische Wochenschrift* 1911, p. 561.

Henius, *Münchener medizinische Wochenschrift* 1911, p. 2221. —

Compare A. Jaquet, *Münchener medizinische Wochenschrift* 1911, p. 2564.

of extract of male fern, as advised by Drenkhahn, entails some danger, and also that the extract should not be administered in capsules, as their solution in the gastro-intestinal tract cannot be relied upon. The author prefers the method suggested by Boas of prescribing the extract in the form of an emulsion. In his experience doses of 8 grammes (140 min.) are sufficient. He is, however, in favour of the avoidance of castor oil and considers a bitter water to be the most suitable aperient to take in conjunction with male fern. But it should not be given sooner than 6 hours after the extract, so that the tapeworm may be submitted to the action of the poison for a sufficiently long period and that the action of the poison may not be weakened by the laxative. The only question is, whether this method does not provide the possibility of poisoning on account of the length of time during which the extract of male fern remains in the system, and the increased absorption of filicic acid, in persons susceptible to filix poisoning.

According to Lanara, a new indication for extract of male fern, which, however, still requires confirmation, is presented by local skin diseases, such as acute and chronic eczema, seborrhœic eczema, acne, sycosis, etc. Even in chronic, obstinate cases the author states that he has obtained excellent results by painting with the extract. For the local application of the drug in acute affections, he used a solution of 1 part of the extract in 2 parts of ethereal tincture of valerian, and for chronic and subacute cases a similar solution in the proportion of 1 in 0.5 to 1. The solution was applied in the evening, and in the morning the area of skin which had been treated was cleansed with soap and covered with lead and glycerin ointment. In acute eczema the author first applied warm compresses of water or lead lotion for a few days, and he always removed all scabs.

### Malyt.

According to H. Leyden, malyt, in addition to those album preparations which are well absorbed, is useful as a tonic and stimulant in cases of debility. In some cases it is even

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Lanara, Journal des praticiens 1910, No. 5. — Monatshefte für praktische Dermatologie 1910, Vol. 51, p. 189.

Leyden, Fortschritte der Medizin 1911, No. 4.

superior to these preparations, especially when the prolonged employment of preparations of albumose has given rise to diarrhœa; or if, as in febrile conditions, the absorption of albumin and fat has been more or less arrested. In such cases maltyl is more suitable than are preparations of albumin, at it forms a substitute for the increased tissue waste. Leyden had the opportunity of studying the effect of maltyl on anæmic school children of 6 to 9 years of age, who on account of irrational home treatment were weakly and poorly developed. Albuminous and iron drugs were, according to the author, unsatisfactory in action and were not always well taken, whereas maltyl\*) has a pleasant taste and offers a better guarantee of being taken. For this reason Leyden obtained very satisfactory results in the majority of cases in spite of the careless nursing and the questionable hygienic conditions which are so often found among the poor. The observations were carried out on 26 children over a period of 3 to 4 weeks. On account of the anæmic condition prevalent among his patients, the author prescribed triferrin-maltyl, of which a small teaspoonful was taken 3 times a day after meals. The results were as follows: The preparation was always well taken and gave rise to no digestive disturbances; indeed, if digestive disturbances were present they were improved and the appetite was increased in almost every case. General languor, headaches, etc., disappeared, the children became brighter, their appearance improved, the mucous membranes became less pale, and if an irritating cough was present it was relieved. The increase in weight varied between 1 and 3 pounds. Two women, who had become debilitated in consequence of abdominal trouble, were also given triferrin-maltyl (1 tablespoonful 3 times a day) and in the course of 8 weeks gained 4 to 5 pounds with perfect restitution of the general health and strength.

### Manna.

According to E. Otto, many physicians complain of the faulty pharmaceutical technique owing to which most pills become so hard after being stored for a short time that they are either partially or wholly insoluble in the stomach and are thus rendered inert. On the other hand, as pills are

\*) Maltyl is dried malt extract containing about 85 p. c. of carbohydrates and with a high content of diastase.

Otto, Münchener medizinische Wochenschrift 1911, p. 1799.

a favourite form of drug, an innocuous addition which prevents this fault would be welcome, so long as the pills did not alter in shape on keeping nor lose their consistence. For this purpose the author suggests the use of manna electa, of which 5 grammes (75 grains) are added for every 100 pills. He also recommends the use of extractum gentianæ spissum for the same purpose. These two additions are said to have fulfilled their purpose very well.

### Maretin.

A résumé of the reports on this antipyretic\*), which has been variously criticised in the literature, has been published by Schmitz. He came to the conclusion that the drug should under all circumstances be administered to patients suffering from febrile phthisis or from typhoid 1 to 2 hours before the expected rise in temperature. The absence of fever usually lasts half a day, or longer. If rationally used, secondary effects, especially the sweats of phthisical patients, can be safely avoided, provided the patients be not otherwise disposed to them. The author advises the use of 0.1 to 0.2 gramme ( $1\frac{1}{2}$ —3 grains) as a single dose, but believes that this dose may be exceeded in rheumatic subjects (acute articular rheumatism). 0.5 gramme ( $7\frac{1}{2}$  grains) is considered the maximum daily dose. The yellow tint of the skin and the discoloration of the urine sometimes observed after the employment of maretin are due to an absolutely harmless dye, which is formed in the organism by the oxidation of maretin.

The controversy between W. Heubner and H. Dreser with regard to maretin (its harmfulness or harmlessness) can only be mentioned here. It may be noted that Heubner fears that the prolonged administration of the preparation may give rise to anæmic conditions; these would be more apt to occur as there is a very narrow margin between the efficacious dose and the dose which gives rise to anæmia.

### Mastic.

Thomschke tested the mastic solution (20 grammes of mastic, 50 grammes of chloroform, 20 drops of linseed oil)

\*) Compare Merck's Reports 1904—1908.

Schnitz, Fortschritte der Medizin 1910, No. 43.

Heubner, Therapeutische Monatshefte 1911, No. 6 and 8.

Dreser, Therapeutische Monatshefte 1911, No. 8.

Thomschke, Münchener medizinische Wochenschrift 1911, p. 686.

suggested by von Oettingen, in a large number of surgical operations and wounds, and expresses himself well satisfied as to its practical value. A mastic dressing is not only cheaper than other dressings, but is easier to apply and yet fulfils all the requirements of modern technique. I have described the technical side of this dressing in sufficient detail before\*), and shall not therefore refer in detail to Thomschke's communication. The possible irritant symptoms due to mastic may, however, be considered. According to the author, they are rarely observed provided the solution be correctly employed. The smallest possible quantity should be used, in order that it may not soak through the gauze dressing. In very sensitive persons, chiefly women, irritant skin lesions occasionally occur; in these cases this method, otherwise so practical, must be abandoned. Haist recommends as a wound dressing the simultaneous application of iodine and mastic solution. According to his instructions, the neighbourhood of the wound is painted first with tincture of iodine and then with mastic solution, whereupon the wound is covered with a sterile dressing.

As the cutaneous irritation has been attributed to the chloroform in the mastic solution mentioned above, F. W. Voos used the so-called "mastisol", a solution of mastic in benzol\*\*), which offers the same advantages and is even said to possess greater adhesive power. It is used as follows: In all injuries, cuts, bullet wounds, contused wounds with ragged edges, and compound fractures, the neighbourhood of the wound is painted with mastisol up to the very edge of the wound, without regard to the degree of soiling and without previous cleansing; by this means all the bacteria present on the skin are fixed and rendered innocuous. Very dirty wounds are freed from foreign bodies by means of forceps or a swab, after which the aseptic dressing is applied; this immediately adheres to the parts which have been painted and cannot be displaced. In the case of smaller wounds the dressing keeps in place without special methods of fastening

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Oettingen, Merck's Report 1906.

\*) Compare Merck's Reports 1906 and 1910.

Haist, Deutsche militärärztliche Zeitschrift 1911, No. 19.

Voos, Münchener medizinische Wochenschrift 1911, p. 688.

\*\*) It should be noted that this solution of mastic is inflammable as compared with the solution in chloroform.

with bandages, etc., and this is specially convenient for the hands, fingers and face. The advantages of mastisol dressings are also confirmed by Börner and Mazel.

### Menthol.

V. Vohryzek used the menthol solution recommended by Berliner with good results in the treatment of pulmonary tuberculosis. It consists of 10 grammes ( $\frac{1}{3}$  oz) of menthol and 30 grammes (1 oz) of dericin oil (or 10 grammes ( $\frac{1}{3}$  oz) of menthol, 20 grammes ( $\frac{2}{3}$  oz) of eucalyptol and 100 grammes ( $3\frac{1}{3}$  oz) of dericin oil) and is injected intramuscularly in single doses of 1 c.c. (17 min.). It is said to be relatively non-poisonous, painless and strongly bactericidal. In about 100 cases, from slight apical affections to advanced phthisis, Vohryzek used menthol with such good results, that, in his opinion, it surpasses all other drugs in improving the general health in cases of tuberculosis.

As an inhalation for laryngitis, bronchitis and nasal catarrh, M. Berliner recommends a mixture of 2 grammes (30 grains) of menthol, 2 grammes (34 min.) of eucalyptus oil, 1 gramme (17 min.) of oil of anise, and 5 grammes (100 min.) of alcohol, and Müller a mixture of 1 gramme (15 grains) of menthol, 1 gramme (17 min.) of lysoform and 3 grammes (55 min.) of alcohol (so-called lysomenth). These compounds must be inhaled by means of a suitable spray.

Menthol, which others have recommended for the treatment of insect stings, is prescribed by K. F. Hoffmann for mosquito bites as follows:

Rp. Menthol	0.2 gramme (3 grains)
Terebinth. laric.	
Ol. ricin.	aa 1.0 gramme (15 grains)
Collod. dupl.	18.0 grammes (270 grains)

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- Börner, Münchener medizinische Wochenschrift 1911, p. 2272.  
 Mazel, Das Mastisol und seine Anwendungsweisen. Vienna 1911,  
 Published by M. Perles. — Der Militärarzt 1911. (Wiener  
 medizinische Wochenschrift No. 20 and 21.)  
 Vohryzek, Klinisch-therapeutische Wochenschrift 1911, p. 369.  
 Berliner, Berliner klinische Wochenschrift 1910, p. 967; compare  
 Merck's Report 1910, p. 174.  
 Berliner, Ärztliche Polytechnik 1911, No. 1.  
 Müller, Therapie der Gegenwart 1911, p. 47.  
 Hoffmann, Münchener medizinische Wochenschrift 1911, p. 1080.

Another preparation which may be mentioned here is the so-called "dioradin", a combination of menthol, iodine and radium. A. von Szendeffy carried out the first trials with this preparation, which showed it to be excellent in the treatment of tuberculosis. This is confirmed in the detailed communications of S. Bernheim and L. Dieupart, and in a treatise by L. Robinson. Dioradin, according to these authors, is a radio-active iodine-menthol, which consists of 0.75 centigramme of peptonised iodine, 0.06 centigramme of menthol and 0.1 drop of ethereal radium-barium chloride solution. This probably signifies the amount of a single dose for intramuscular injection. The treatment of tuberculosis by means of this drug is said to be comparatively simple. It consists in the administration of up to 4 series of dioradin injections. On 10 consecutive days a daily injection of 1 c.c. is given into the right and left arm alternately, or into the gluteal region; then on alternate days a series of up to 30 or 40 injections, after which an interval of 8 to 14 days is allowed to elapse. The site of the injection must be disinfected by means of corrosive sublimate solution to prevent local irritative symptoms. Should iodism occur, the employment of the drug must be interrupted. Cardiac and renal affections are at present considered contra-indications to its use. In all forms of tuberculosis dioradin treatment is said to have proved of good service, especially in the first and second stages of the disease. But before introducing the drug into general practice, it will be best to await further clinical confirmation.

### Mercuric Sulphide, Red

F. Hubbes is trying to re-introduce the now obsolete fumigation with cinnabar in the treatment of syphilis. The author is convinced that mercury renders all other drugs superfluous, if only it be correctly used. This, in his opinion, is the case if the mercury be inhaled in a nascent state. For this purpose cinnabar is heated with powdered iron to

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Bernheim-Dieupart, *Zeitschrift für Tuberkulose* 1911, Vol. 17, No. 5, p. 440. — *Petersburger medizinische Wochenschrift* 1911, p. 278. — *Pester medizinisch-chirurgische Presse* 1911, No. 25 to 45. — *Nouveaux remèdes* 1911, p. 313.

Robinson, *British Medical Journal* 1911, 8<sup>th</sup> July, p. 66.

Hubbes, *Münchener medizinische Wochenschrift* 1911, p. 360.

bind the sulphur, in order that it may not be oxidised and in the form of sulphur dioxide annoy the patient. The mercury vapours thus formed must be inhaled immediately, before losing their chemical properties (?). "The mercury is then probably combined, on account of its greater affinity, with the hæmoglobin of the blood, forming an intense poison for spirochetes, which is carried to the most distant parts of the body. The results at least point to this action, for by means of 8 to 10 inhalations, carried out on 4 to 5 days, I have been able to cure the severest cases of lues without recurrence. As the cure occupies such a short time, and even the severest symptoms disappear within 10 to 14 days, without the necessity of any treatment after the inhalations, I think the treatment may correctly be called a rapid cure." The well known secondary symptoms of mercury cures (stomatitis) are also liable to occur. But as the means of avoiding these secondary effects are known, the author hopes that his method of treating syphilis may prove a blessing to mankind.

#### Mercurous Nitrate.

As is well known, Jefimow used Liquor Bellosti, a solution of 1 gramme of mercurous nitrate in 8 grammes of water and 2 grammes of nitric acid, as a test for helminthiasis, and Butenko used it as a diagnostic for paralysis, as the substances excreted in the urine in these diseases are said to be either stained black or precipitated by the reagent. The diagnostic value of Jefimow's reaction was doubted by Marku. Recently, the investigations of A. Trapet and F. Wolter, H. Cohn and H. M. Stucken have also laid the value of Butenko's test open to doubt.

Trapet and Wolter found that Butenko's reaction occurred in many cases of non-paralytic and healthy persons, so that it did not offer a reliable means of demonstrating the presence

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Jefimow, *Zentralblatt für Kinderheilkunde* 1907, p. 152. — Merck's Report 1907, p. 127.

Butenko, *Russkij Wratsch* 1910, No. 2. — *Italia sanitaria* 1910, p. 303. — *Rivista critica di clinica medica*, Vol. 11, 31. — Merck's Report 1910, p. 213.

Marku, communicated by Stucken.

Trapet-Wolter, *Psychiatrisch-Neurologische Wochenschrift* 1911, No. 48.

Cohn, *Psychiatrisch-Neurologische Wochenschrift* 1911, No. 2.

Stucken, *Münchener medizinische Wochenschrift* 1911, p. 855.

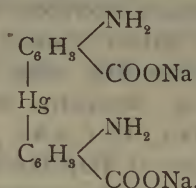
of paralysis, although it is more often present in paralytics than in non-paralytics. Cohn also denies the diagnostic value of Butenko's reaction.

Stucken, after careful investigations, came to the following conclusions: In some urines, both those of patients severely ill and of apparently healthy ones, blackening of the sediment occurs on heating with mercurous nitrate in a dilute solution of nitric acid, probably being due to reduction. This reaction is not specific for any disease. The reacting substance is stable towards heat, very sensitive to acid, insoluble in ether. The author proposes to continue his investigations as to the chemical nature of the substance in question.

### Mercury Dicarboxylic Acids, Aromatic

F. Blumenthal describes two aromatic mercury dicarboxylic acids, the properties and action of which have a certain amount of therapeutic value, viz., diamino-diphenyl-mercuri-dicarboxylic acid, and sodium dinitro-diphenyl-mercuri-dicarboxylate.

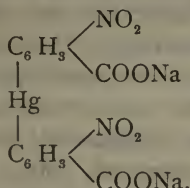
Sodium diamino-diphenyl-mercuri-dicarboxylate is a white or yellowish, crystalline powder, readily soluble in water. Its solutions are yellow or brown in colour and do not precipitate albumins. The preparation contains 38 p. c. of mercury; its chemical formula is as follows:



The salt has proved relatively non-toxic in experiments on animals, for a rabbit weighing 2 to 2.5 kilogrammes can take 1 gramme without showing evidence of illness, whereas with corrosive sublimate this only occurs when the dose does not exceed 0.02 gramme. The animal organism can therefore stand about 20 times as much mercury in the form of the new mercury compound than of corrosive sublimate. Besides, the author confirmed the fact that the preparation, when given internally or subcutaneously in relatively large doses,

occasions no intestinal irritation, no local symptoms of irritation and in conformity with its chemical relationship to orthoform, most probably no pain. When given by mouth most of it is absorbed. It has, unlike corrosive sublimate, no antiseptic action in vitro.

Sodium dinitro-diphenyl-mercuri-dicarbo-nate corresponds entirely with the diamino preparation as regards non-toxicity and biochemical behaviour. It forms a yellow, crystalline powder, readily soluble in hot water, and corresponds to the following chemical formula:



For subcutaneous injection in his pharmacological experiments, Blumenthal used a 5 p. c. solution, in which part of the salt crystallises out on cooling. His experiments showed that a strong spirilloicide action is characteristic of sodium dinitro-diphenyl-mercuri-dicarbonate. In experiments on rabbits one or two injections of an amount of the dinitro-salt far below the toxic dose sufficed to bring about the disappearance of the spirochetes in a few days and to cure the clinical symptoms.

### Mercury Glidine.

This preparation, formerly described by Neuberg and Piorkowsky under the designation of "luesan", and which, according to M. Lewitt, J. Matsumoto and R. Frühwald represents a lecithin-albumin containing mercury, is only put on the market in the form of tablets, which are said to contain 0.005 or 0.01 gramme ( $\frac{1}{12}$  or  $\frac{1}{6}$  grain) of mercury and are only intended for internal use. Matsumoto and Frühwald have tested this drug in a fairly large number of cases of syphilis and express the following opinion as to its action:

Neuberg, *Therapeutische Monatshefte* 1908, p. 580. — Compare

*Vierteljahresschrift für praktische Pharmazie* 1908, p. 306.

Piorkowsky, *Allgemeine medizinische Zentralzeitung* 1909, No. 5.

Lewitt, *Fortschritte der Medizin* 1911, No. 42.

Matsumoto-Frühwald, *Klinisch-therapeutische Wochenschrift* 1911, No. 10—12.

Mercury glidine acts promptly, especially in secondary syphilis, and particularly on the cutaneous symptoms, which rapidly disappear under its action. This takes longer, as is usually the case with internal mercury medication, than when mercury is applied by inunction or injection. Severe forms of syphilis offer even greater resistance to mercury glidine treatment, although these also can be completely cured. Therefore the treatment is certainly not suitable for very severe and threatening forms of syphilis and in these forms will be unable to replace the external methods of mercury application. But if the latter are inapplicable for any reason, mercury glidine may be used with advantage. It is usually well tolerated. In a third of the cases the administration at first certainly caused diarrhoea, but this was readily controlled by opium. In a few cases transient abdominal pain, vomiting and mild stomatitis were also observed, but the general condition remained good and albuminuria never occurred. The dose consisted at first of 3, and after a week of 6 tablets a day. The total number of tablets administered varied according to the severity and extent of the syphilitic symptoms, the greatest number being 613, corresponding to 3.735 grammes of mercury. The authors were unable to discover any difference in the action of the stronger and the weaker tablets.

### Mercury Guaiacol-Sulphonate.

The mercuric salt of orthoguaiacol-sulphonic acid,  $\text{Hg}(\text{C}_6\text{H}_3 \cdot \text{OH} \cdot \text{OCH}_3 \cdot \text{SO}_3)_2$ , according to R. Horand, forms brown crystals, readily soluble in water, and which can be sterilised in aqueous solution without decomposition. It is therefore most suitable for the treatment of syphilis. Most important, according to Horand, is the intramuscular injection of this preparation. Before commencing its use, as with all mercury cures, the kidneys, gums and buccal mucous membrane must be examined. Small doses of 0.02 gramme ( $\frac{1}{3}$  grain) in aqueous sterile solution are used at first and are best injected into the gluteal region; thus the patient's tolerance for mercury can be determined. An injection is given on alternate days, or in urgent cases daily, up to 10 or 20 injections, after which an interval of 10 days is allowed. If

the patient bears the preparation well, which is in the author's experience usually the case, the dose is gradually increased to 0.06 gramme (1 grain) (in 1 c.c. [17 min.] of water). In the first year of treatment 12 series of injections, each consisting of 10 injections, should be given. This treatment is said to have proved useful in all stages of syphilis. Occasionally the action is very rapid. Thus Horand, in a patient suffering from extensive papulation of the mucous membranes and headache coupled with sleeplessness, brought about the disappearance of all the symptoms by an injection of 0.06 gramme (1 grain); and in a case in which salvarsan was not tolerated he effected a considerable improvement by 3 injections of 0.02 gramme ( $\frac{1}{3}$  grain). Horand states that he has never observed symptoms of intolerance and he therefore advises the introduction of this new mercury salt into the treatment of syphilis. It may be noted that mercury guaiacol-sulphonate can also be used internally in the form of solutions or tablets. As it contains 33 p.c. of mercury, Horand reckons that a single dose for an adult should be 0.06 to 0.12 gramme (1—2 grains).

### Mercury Oxycyanide.

For the treatment of pertussis W. Münch recommends a 0.1 p.c. solution of mercury oxycyanide:

Rp. Hydrarg. oxycyanid. 0.01 gramme ( $\frac{1}{6}$  grain)

Aq. destill. 10.0 grammes ( $\frac{1}{3}$  oz)

(To be dispensed in a drop bottle.)

Of this 3 drops are prescribed every 2 hours for babies, and for older children 5 to 10 drops, to be given in tea. As an auxiliary to this treatment, he prescribed inhalations of naphthalene fumes; a ball of naphthalene was placed in a metal dish as near to the patient as possible, and heated so that fumes were given off. The result was, as a rule, soon evident by a diminution in the number and duration of the attacks of coughing. Besides the medicinal treatment, diet, massage and baths were taken into consideration.

As recently glycerin mixtures (soluble in water), sterilised and kept in special glass vessels, have come into use as lubricants for catheters, A. Strauss suggests a suitable mix-

ture for this purpose which, as it contains mercury oxycyanide, remains sterile, even though it be not kept in special vessels. The formula is:

Rp. Tragacanth.	1.6 grammes (25 grains)
tere cum aqua frig.	50.0 grammes ( $1\frac{2}{3}$ oz)
Glycerin.	ad 100.0 grammes ( $3\frac{1}{3}$ oz)
coque ad sterilisat.	
Hydrarg. oxycyanid.	0.1 gramme ( $1\frac{1}{2}$ grains)

A similar lubricant has been recommended before for anæsthetising the urethra. This, according to E. Grätzer, consists of: 13.0 grammes (195 grains) of tragacanth, 36.0 grammes (1 oz) of glycerin, 370.0 grammes ( $12\frac{1}{3}$  oz) of distilled water, 21.0 grammes (315 grains) of alypin and 1.0 gramme (15 grains) of mercury oxycyanide, and is to be introduced by means of the Ultzmann ointment syringe.

### Mercury Salicylate.

Dreuw again reports on the technique of injections of mercury salicylate. Last year I alluded to a suggestion of his, which may prove of use if the injection needle becomes blocked by emulsions of mercury salicylate and paraffin\*). The modified suggestion of Dreuw is as follows: "The cannula should be wrapped in cotton wool, and introduced upside down into the Pravaz syringe, a finger is pressed over the cannula and the piston of the Pravaz syringe, which has been previously filled, is pressed down."

In order to avoid pain after the injection of mercury salicylate and paraffin emulsion, the author recommends the use of a special needle. Assuming that the pains after the injection are due to the sudden distribution of the mercury salicylate at the same spot, he experimented with a needle which was closed at the point and had 5 to 10 lateral apertures. The emulsion is pressed out through these and thus simultaneously reaches different parts of the tissue. By this means, according to Dreuw, the pains both during and after the injection are diminished, although not totally removed. As by the use of an injection needle of this description

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Grätzer, Deutsche medizinische Wochenschrift 1911, p. 376.  
(Compare Folia urologica, March 1910.)

Dreuw, Monatshefte für praktische Dermatologie 1911, Vol. 52, p. 304.

\*) Compare Merck's Report 1910.

the absorption of the substance injected extends over a larger area, it might also prove useful for injecting other drugs, such as morphine solution and camphorated oil.

### Mergal.

According to J. Lechtmann, mergal is an internal antisymphilitic, which brings about the comparatively rapid disappearance of visible syphilitic manifestations, and only gives rise to slight by-effects. As a combination of salvarsan and preparations of mercury has recently been recommended by various observers, the author expects good results from the simultaneous use of salvarsan and mergal. In place of the treatment of the buccal cavity with potassium chlorate, as is customary in mercury cures, the author suggests the employment of givasan paste, which, if correctly used, prevents the occurrence of stomatitis mercurialis.

Ivezic has also obtained highly satisfactory results by the employment of mergal. Fresh cases of lues, even those with primary lesions, were very favourably influenced by mergal medication. All secondary lesions disappeared in 4 to 5 weeks. During their stay in hospital, the patients were given on an average 300 mergal capsules, and were further treated as out-patients\*).

### Merjodin.

J. Odstrcil treated his syphilitic patients by giving them 2 merjodin\*\*) tablets a day at first, and increasing the amount by one tablet daily after the third day, until a daily dose of 9 to 12 tablets had been reached. In the same way and at the same intervals he diminished the dose to 2 tablets. The smallest number of tablets used per patient was 158, and the greatest number 426. Merjodin tablets are best taken in water after meals. Provided acid foods be eschewed, the author states that digestive disturbances never occur. Odstrcil only rarely heard a patient complain of slight gastric trouble. A few patients were troubled with painful diarrhoea, which

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Lechtmann, *Der praktische Arzt* 1911, No. 2.

Ivezic, *Monatshefte für praktische Dermatologie* 1911, Vol. 53, p. 410.

\*) Compare Merck's Reports 1906–1910.

Odstrcil, *Klinisch-therapeutische Wochenschrift* 1911, p. 604.

\*\*) Compare Merck's Report 1910.

ceased in 16 to 22 hours, after the administration of bismuth and opium. Artificial exanthemata never occurred, and with proper care of the mouth slight stomatitis was only rarely observed. Whereas in treatment by inunction the author had frequently noticed considerable loss of weight, by the use of merjodin, as indeed in all methods of internal treatment with mercury, he only observed a slight loss of weight. He treated hard sores by covering one part with sterile strips of gauze soaked in normal saline solution and the other part with ointment or dusting powder containing 5 to 10 p.c. of soziodol-mercury. In favourable cases the sores healed in 12 to 16 days. Even after 2 to 3 days no more spirochetes were to be found. In 10 cases of syphilitic roseola the rash disappeared in 8 to 10 days by treatment with merjodin. Large macular syphilides, which usually appeared 2 to 3 years after infection, healed in a fortnight; small and large papular syphilides required 6 to 7 weeks for their involution; while the moist papules on the genitals and the broad condylomata round the anus were healed in 4 weeks, or in severe cases in 7 weeks. These efflorescences were treated locally with benzine or solution of hydrogen peroxide, or with an 8 to 10 p.c. soziodol-mercury ointment. Merjodin medication was also very useful in syphilitic affections of the pharynx, in psoriasis of the palms and soles, after operations on suppurating inguinal glands, and in fibrous orchitis.

M. von Zeissl uses merjodin in those cases which show a recurrence after treatment with salvarsan, or in which treatment with salvarsan or with subcutaneous injections of mercury cannot be carried out. He has obtained good results by this means.

### Mesotan.

As is well known, attempts have been made to avoid the cutaneous irritation which has frequently been observed to follow the employment of mesotan\*) by diluting the preparation with olive oil or vaseline, and this measure has, in the majority of cases, proved successful. Recently, mesotan has been put on the market in the form of a cream, which, accord-

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von Zeissl, Wiener klinische Rundschau 1911, p. 287.

\*) Compare Merck's Reports 1902—1907.

ing to Hecht, Klein and Weil, appears to give rise to no cutaneous symptoms. Mesotan cream is a 20 p.c. mesotan ointment mixed with a small quantity of stearin, which causes retardation of its absorption and decomposition, without injuring the recognised good therapeutic action of mesotan. Weil even used mesotan cream for massage in a number of cases without observing a single case of cutaneous injury. The drug is useful in lumbago, muscular rheumatism, articular rheumatism, neuritis in a rheumatic subject, erysipelas, and various joint swellings. As much is rubbed into the skin in the morning and evening as the area under treatment will absorb. The seat of application is varied daily by rubbing the drug into the painful region itself one day, and into its immediate vicinity the next day.

### Mesothorium.

Mesothorium, which is issued in the form of mesothorium bromide, was discovered in 1907 by O. Hahn in the course of his investigations on the products of transformation of thorium. According to the author, it is the first product of disintegration of thorium and the mother-substance of radiothorium\*), which was discovered 2 years earlier. In its chemical properties it is identical with radium and barium, but

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Hecht, *Geneeskundige Courant* 1909, No. 30.

Klein, *Deutsche medizinische Wochenschrift* 1910, No. 48.

Weil, *Münchener medizinische Wochenschrift* 1911, No. 9.

Hahn, *Berichte der deutschen chemischen Gesellschaft Berlin* 1907, Vol. 40, p. 1464 and 3304; *Physikalische Zeitschrift* 1908, Vol. 9, p. 248 and 392; 1910, Vol. 11, p. 493, Vol. 12, p. 468. — Compare also: McCoy and Ross, *Journal of the American Chemical Society* 1908, Vol. 29, p. 1709; Hoffmann, *Physikalische Zeitschrift* 1907, Vol. 8, p. 553; Marckwald, *Berichte der deutschen chemischen Gesellschaft Berlin* 1911, Vol. 43, p. 3420; Russel and Soddy, *Philosophical Magazine* 1911, Vol. 21, p. 130; Soddy, *Journal of the Chemical Society* 1911, Vol. 99, p. 72; Hahn, *Chemiker-Zeitung* 1911, p. 845.

\*) Compare Hahn, *Zeitschrift für physikalische Chemie* 1905, Vol. 51, p. 717; *Berichte der deutschen chemischen Gesellschaft Berlin* 1905, Vol. 38, p. 3371; Blan, *Atti della reale accademia dei Lincei Roma* 1906, Vol. 15, I, p. 349 and *Physikalische Zeitschrift* 1906, Vol. 7, p. 620; McCoy and Ross, *Silliman's American Journal of Sciences* 1906, Vol. 21, p. 433; Ramsay, *Journal de chimie et de physique* 1905, Vol. 3, p. 617; Rutherford and Hahn, *Philosophical Magazine* 1906, Vol. 11, p. 793 and Vol. 12, p. 371.

differs from them in its physical properties, especially in its power of radiation, and intensity of radiation. Technically prepared mesothorium always contains radium, the amount varying according to the uranium content of the original substance, the Monazite sand found in Brazil; the radium is responsible for about a quarter of the activity of technical mesothorium. As for radium, so for mesothorium the emanation on the one hand, and on the other hand the  $\alpha$ ,  $\beta$  and  $\gamma$  rays, which are emitted by mesothorium as well as by radium, are of therapeutic use. It may therefore be expected that mesothorium will be used for therapeutic purposes as a substitute for radium, which is so difficult to obtain.

Of the 3 varieties of mesothorium rays (or mesothorium bromide) mentioned above, the  $\beta$  and  $\gamma$  rays penetrate glass and a not too thick mica plate, while the  $\alpha$  rays and the emanations are held back by these substances. A. Bickel and Minami relied on these properties of the different rays in their experiments on the activation of autolytic ferments by their means. As is known, it had been previously proved by various authors that ferments can be activated under the influence of radium radiations. The authors now found that activation of this nature did not occur in carcinoma, sarcoma and normal dog's liver under the influence of the  $\beta$  and  $\gamma$  rays of mesothorium, and they concluded, taking for granted the identical action of radium and mesothorium rays, that the activation of ferments must be entirely a property of the  $\alpha$  rays and the emanation. In the investigation of digestive ferments, also (pepsin, diastase, pancreatin), Minami found that the  $\beta$  and  $\gamma$  rays of mesothorium exerted at the most a negligible and transitory influence on these ferments, and that this influence was at times one of activation and at times one of arrest of the fermentative action. The same authors also showed that the  $\beta$  and  $\gamma$  rays of mesothorium bring about the same tissue changes in human skin as do the corresponding radium rays. In agreement with this is the result obtained by G. Baum in a case of cancrioid of the skin which he treated by mesothorium radiation, and from which he concluded that mesothorium preparations are little inferior to radium preparations as regards their thera-

Bickel-Minami, Berliner klinische Wochenschrift 1911, p. 1413.

Minami, Berliner klinische Wochenschrift 1911, p. 1798.

Baum, Berliner klinische Wochenschrift 1911, p. 1594.

peutic utility. In his experiments he used mesothorium in capsules, the mesothorium being protected by a mica plate. Thus only the  $\beta$  and  $\gamma$  rays could act. In several cases of nævi and lupus mesothorium radiation also proved effectual.

O. Emsmann carried out experiments with mesothorium emanation. From his results the conclusion may be drawn that this emanation is identical or similar in action to radium emanation.

### Metaferrin.

A new iron-albumin preparation containing phosphoric acid and with a content of 10 p.c. of iron, has been described by L. Januszkiewicz, H. Voit and W. Bettinger. This is metaferrin, a light brown, odourless powder, with a slightly acid taste; it is insoluble in water and hydrochloric acid (in the dilution of the gastric juice). It is, however, soluble in alkalies. It thus passes through the stomach unchanged and is dissolved in, and absorbed from the intestine. Thus the stomach is not burdened by the metaferrin and the drug is consequently well tolerated even by the most debilitated patients. According to Januszkiewicz, retention of fæces was caused in 2 persons inclined to constipation, whereas Bettinger states that he has more often observed that metaferrin stimulates peristalsis. The action of the preparation is apparent in an increase in the hæmoglobin content, an increase in weight, improvement in the general health, and, if taken before meals, an increase in the appetite. Metaferrin treatment is best carried out by giving at first 3 tablets (0.25 gramme [4 grains] each) a day, increasing the amount by 1 tablet every 4 days, until 6 tablets are taken during the day, and returning in a similar way to the original dose.

With the addition of 0.1 p.c. of arsenic the preparation is known as "arsen-metaferrin". It is used in the same way and in the same doses as metaferrin. Both drugs are put on the market in a fluid form under the designations "metaferrose" and "arsen-metaferrose". They are given in tablespoonful doses. In the fluid form of these drugs the advantage of insolubility of metaferrin is naturally lost. Voit

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Emsmann, Berliner klinische Wochenschrift 1911, p. 2108.

Januszkiewicz, Medizinische Klinik 1911, p. 1123.

Voit, Therapie der Gegenwart 1911, p. 431.

Bettinger, Zentralblatt für die gesamte Therapie 1911, p. 505.

states that he has more often heard complaints of slight gastric disturbances after the administration of metaferrose than is the case after metaferrin.

The indications for metaferrin and arsen-metaferrin are the same as for iron, e. g., anæmias, chlorosis, during convalescence, etc.

### Methylene Blue.

V. Audibert and Rouslacroix, on the ground of their experiments, expect to obtain good results in Malta fever by the employment of methylene blue. After the administration of the drug in 2 cases they observed an immediate fall in the temperature. As the medication is harmless and is also said to have a sedative action, further tests of the method described by the authors may be recommended. 0.05 gramme ( $\frac{3}{4}$  grain) of methylene blue in capsules is given 2 to 3 times a day, and if they are not well tolerated by the stomach, it is given mixed with 0.25 gramme (4 grains) of lactose. In continuous vomiting methylene blue may be injected subcutaneously dissolved in 1 c.c. (17 min.) of water. The communications of the above named authors induced d'Oelsnitz and Boinet to try the effect of methylene blue in Malta fever; but their results were not satisfactory in spite of increased dosage (0.1 gramme [ $1\frac{1}{2}$  grains]).

In order to demonstrate the ramifications of rectal fistulæ, J. Lynch employs a solution of methylene blue in solution of hydrogen peroxide. The oxygen given off by the decomposition of the latter is said to assist in driving the colouring matter into the finest ramifications of the fistula and thus render them evident.

J. Fuchs and W. Lintz describe a reaction of urine which occurs in a variety of diseases, especially in carcinoma, sarcoma, and in an advanced stage of pregnancy, and which is also occasionally observed in renal affections, tuberculous meningitis, endocarditis, rheumatism, abortion, etc. It depends upon the discoloration of methylene blue and in spite of its

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Audibert-Rouslacroix, *Presse médicale* 1911, No. 2.

d'Oelsnitz, *Revue internationale de médecine* 1911, p. 260.

Boinet, *Marseille médical* 1911, 15<sup>th</sup> June.

Lynch, *Medical Record* 1911, 3<sup>rd</sup> June.

Fuchs-Lintz, *Journal of the American Medical Association* 1911, Vol. 56, p. 1882.

many indications it is said to be of use as a characteristic reaction for malignant tumours. The best solution to use is the so-called Löffler's methylene blue\*), with which the urine to be tested is coloured blue (3 to 5 drops of methylene blue). If the reaction is positive, the blue coloration disappears in the course of 12 to 24 hours at the ordinary temperature.

### Microscopic Methods of Staining.

Several new reagents have been recommended by B. Rawitz for the technique of staining the central nervous system; these are in some respects superior to other stains at present in use. The author's formol-fuchsin is prepared by dissolving 4 grammes of fuchsin (large crystals) in 100 c.c. of 95 p.c. alcohol, 100 c.c. of water and 20 c.c. of formaldehyde (40 p.c.). It will keep for an indefinite period and should be diluted before use with 25 to 50 volumes of water. The sections are left for 24 hours in this stain, are then rapidly washed in water and placed in a solution of tartar emetic in 95 p.c. alcohol saturated at the ordinary temperature; this fixes the stain in the tissue under treatment. Other organic stains, such as methyl violet, malachite green, methyl green, methylene blue, etc., when combined with formaldehyde as described above, are said to be inferior as regards their staining power to fuchsin.

Well stained specimens of the central nervous system are also obtained by treating the sections, which have been previously treated and fixed, with the following solutions of azofuchsin G and azofuchsin B, which in the author's experience even form a perfect substitute for carmine solution: 1 gramme of azofuchsin G and 5 grammes of aluminium-ammonium sulphate are dissolved in 100 c.c. of water and 100 c.c. of aqueous picric acid solution saturated in the cold, and the solution is heated to boiling for about 3 minutes in a glass flask. After 24 hours it is filtered. The reagent thus obtained keeps indefinitely. The solution of azofuchsin B is prepared in the same manner and in the same proportions. Azofuchsin B stains with a tinge of blue, azofuchsin G with a tinge of yellow, otherwise the staining characteristics of the two reagents are identical.

\*) Compare Merck's Reagenzien-Verzeichnis 1908, p. 159.  
Rawitz, Zeitschrift für wissenschaftliche Mikroskopie 1911,  
Vol. 28, p. 1.

As a substitute for van Gieson's reagent\*) Rawitz suggests the following solutions.

1. A mixture of 30 c.c. of a 5 p.c. aqueous solution of azofuchsin G and 300 c.c. of aqueous solution of picric acid saturated in the cold.
2. A mixture made up in the same proportions using azofuchsin B.

In place of Burri's Indian ink as a negative stain for bacteria, H. Fischer uses a saturated, aqueous solution of Congo red or Nigrosin. To the freshly heated staining solution a drop of the fluid containing bacteria is added on a slide; the mixture is spread out and allowed to dry, if necessary it is gently warmed. By mounting in Canada balsam a good permanent preparation is obtained. The method depends upon the property possessed by these stains of not penetrating into the bodies of the bacteria.

As a substitute for Löffler's nutrient medium for typhoid, Dennemark suggests a nutrient medium which offers a better view and especially greater transparency. He considers the most suitable stain to be Pure Blue rendered colourless by means of alkali. The discoloration of the necessary amount of 1 p.c. solution of Pure Blue is effected by boiling with 2.5 p.c. solution of caustic soda. The nutrient medium, which consists of 3 p.c. nutrient agar with the addition of 1 p.c. of peptone, 1 p.c. of nutrose, 0.5 p.c. of sodium chloride and 1 p.c. of milk sugar, is exactly neutralised before use, phenolphthalein being used as an indicator; then 5 p.c. colourless Pure Blue solution is added. The material to be examined is spread out in the usual way on the nutrient medium, which has been plated out to a thickness of 2 mm.; it is incubated for 18 to 20 hours and then examined. By transmitted light the typhoid colonies are quite transparent, by reflected light they are of a faint white colour, which is particularly plain against a black background. The larger colonies, when seen in oblique light, show a bright, curiously iridescent, but colourless edge. By the use of the Pure Blue nutrient medium the bacteriological diagnosis of typhoid is said to be rendered comparatively easy and simple.

\*) Compare Merck's Reagenzien-Verzeichnis 1908, p. 90.

Fischer, Zeitschrift für wissenschaftliche Mikroskopie 1911, Vol. 27, p. 475.

Dennemark, Deutsche medizinische Wochenschrift 1911, p. 1023.

Another nutrient medium for typhoid is described by Bitter. This is China Blue-Malachite-Green-agar. According to his directions, 30 grammes of stick-agar are heated for three-quarters of an hour with a mixture of 1 litre of nutrient broth and 7 c.c. of normal hydrochloric acid solution; then 1 p.c. of peptone, 0.5 p.c. of sodium chloride and 2 p.c. of milk sugar are added, and after boiling for a few minutes, the mixture is neutralised with normal caustic soda solution, litmus being used as indicator. To 100 c.c. of this nutrient agar 8 drops of saturated, aqueous China Blue solution and 2.5 c.c. of a 0.1 p.c. Malachite Green solution are added and the mixture is sterilised by steam. On this nutrient medium bacillus coli forms vivid blue colonies, typhoid and paratyphoid bacilli colourless, translucent colonies.

O. Waldmann gives a simple method for staining spores, which is carried out as follows: To a 0.2 p.c., aqueous solution of methylene blue caustic potash solution is added to give a percentage of 0.01. The author always used a freshly prepared reagent; he diluted 1 c.c. of methylene blue solution with 9 c.c. of water in a test-tube and then added 0.2 to 0.3 c.c. of a 0.5 p.c. solution of caustic potash. This strength of alkali is considerably higher than that of Löffler's methylene blue solution. The substance to be examined (spread on a slide) is heated with the reagent for 1 to 2 minutes, washed with water and then faintly stained with carbol-fuchsin. In this way both the enclosed and the free spores are stained bright blue and everything else red.

Lactic acid is used by F. Tobler in microscopic examinations in order to hasten and improve certain iodine reactions. Staining by iodine, which is carried out by means of iodine solutions and forms the favourite stain in the technique of botanical microscopy, especially in mycology, is well known to possess the disadvantage that the iodine being dissolved in alkaline iodides or alcohol, crystals separate out on evaporation of the solvent, thus interfering with the microscopic view and sometimes even, as in the isolichenin reaction, postponing the commencement of the reaction. In these cases lactic acid (specific gravity  $1.22 = 75$  p.c.) is run in under the

Bitter, Münchener medizinische Wochenschrift 1911, p. 709.

Waldmann, Berliner tierärztliche Wochenschrift 1911, p. 258.

Tobler, Zeitschrift für wissenschaftliche Mikroskopie, Vol. 27, p. 366.

coverslip to join the objects which have been placed in alcoholic solution of iodine.

Cresyl-violet (brilliant cresyl-violet) is, according to O. P. Gerber, suitable as a clinical stain, as by its use preparations of sputum, gastric contents and fæces can be stained rapidly and without previous fixation. Cresyl-violet, a condensation product of nitroso-meta-cresol and d-naphthylamine, is a powder which dissolves readily in water and weak acids, and of which a saturated, aqueous solution can be prepared for use. A drop of this solution is placed on a slide and a small particle of the material to be examined is added to it, and after mixing, is covered with a coverslip. The staining of the preparation takes place immediately. The nuclei of the perisperm, bacteria, sarcinæ, yeast, etc., are stained dark bluish, the protoplasm a paler, reddish violet colour. Cresyl-violet is also useful in the staining of urinary sediments and histological preparations and in the staining of pathological fragments of tissue. The chief value of the cresyl-violet stain is that clear microscopic preparations can be very rapidly obtained beside the operating table.

Methylene blue and fuchsin are used by Marie Raskin as a stain for diphtheria bacilli. The stain is made up of 5 c.c. of glacial acetic acid, 95 c.c. of water, 100 c.c. of alcohol (95 p.c.), 4 c.c. of an old saturated aqueous solution of methylene blue and 4 c.c. of Ziehl's carbol-fuchsin solution\*). The polar bodies are stained a deep blue, the rods themselves a bright red and thus the form and structure of the bacilli are exceptionally well shown.

### Morphine Hydrochloride.

In acute coryza, especially if nasal breathing be interfered with, Volland recommends the administration of 10 to 15 drops of a 1 p.c. solution of morphine as an excellent means of treatment. According to him, this affords relief in a short time. In the first place the continuous inclination to sneeze is relieved, then the secretion is remarkably diminished and the pressure in the region of the frontal cavities disappears. It is said that on the following day only very

Gerber, Medizinische Klinik 1911, p. 107.

Raskin, Deutsche medizinische Wochenschrift 1911, p. 2384.

\*) Compare Merck's Reagenzien-Verzeichnis 1908, p. 285.

Volland, Therapeutische Monatshefte 1911, p. 595.

slight symptoms of the "cold" are present. In no case does the "cold" last long, nor are larynx, trachea or bronchi involved.

Dionin affords the same amount of relief as morphine, as is evident from a note in the *Pharmazeutische Zeitung* (1911, p. 871). In the case there reported the patient, after taking a dionin tablet at 5 o'clock in the afternoon and another before going to sleep at night, was entirely relieved of his trouble in the course of 24 hours.

Heubner was also able to convince himself of the property possessed by morphine of diminishing secretion in nasal catarrh. Should the "cold" not disappear after this medication, he states that small doses of morphine should be taken on the following days to prevent the catarrh from spreading to the lower air passages. Even should this have occurred, the employment of morphine is indicated.

### Naphthalene.

On the whole, it is generally accepted that pure naphthalene is a harmless preparation, provided it be not given in too large doses, and any secondary effects occurring on its internal administration are attributed to the employment of impure naphthalene; this view is, however, not entirely shared by Kobert, Lewin and other authorities. A case of naphthalene poisoning with a fatal issue has recently been reported by Prochownik, who has used this hydrocarbon for the treatment of oxyuris in adults and children for 8 years without ill effects. The case was that of a boy, aged 6, who on 2 consecutive days had taken 4 naphthalene powders of 0.25 gramme (4 grains) a day, together with castor oil as a purge. Taken ill with somewhat severe symptoms of poisoning, the child could not be saved in spite of immediate treatment. The autopsy showed a rather large persistent thymus, swelling of the spleen and liver, and swelling of the mesenteric gland as well as cloudy swelling and discoloration of the parenchymatous organs. As, to judge by the literature on the subject, the dose administered was not excessive, the

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Heubner, *Therapeutische Monatshefte* 1911, p. 595.

Kobert, *Intoxikationen* 1906, II., p. 672.

Lewin, *Nebenwirkungen der Arzneimittel* 1899, p. 540.

Prochownik, *Therapeutische Monatshefte* 1911, p. 489. — *Semaine médicale* 1911, p. 519.

toxic action of the naphthalene cannot well be explained without assuming a strong idiosyncrasy to the drug. It is not inconceivable, however, that the castor oil given at the same time may have caused an unusually rapid and complete absorption of the drug. This assumption is all the more probable in that in this case the castor oil had not acted, and had remained a comparatively long time in the system. The question as to whether this case, which may not be an isolated one, gives sufficient ground for ceasing to prescribe naphthalene, or if it should merely be prohibited for children, or if only the simultaneous employment of castor oil should be forbidden and the use of other laxatives recommended, must be left for decision to more competent authorities. Prochownik himself considers it better to prescribe other medicaments in place of naphthalene for diseases due to worms.

### Neutralon.

Neutralon\*), according to the experiments of J. Schlesinger, who has used this preparation for a number of years, has proved most useful in conditions of gastric hyperacidity, hyperchlorhydria, hypersecretion and gastric ulcer. In the author's experience, the drug is best administered on an empty stomach, usually about half to one hour before meals; a teaspoonful is given 3 times a day in a glass of lukewarm water. This treatment does not, as a rule, immediately cause the disappearance of the symptoms due to the acidity, but the action usually appeared after conscientiously carrying out the treatment for many days. Besides the cessation of pain, eructations and vomiting, there was almost always a distinct diminution in the acidity or the flow of gastric secretion, without the occurrence of any troublesome by-effects in the intestines. In hyperchlorhydria in a neurotic subject a combination of neutralon and atropine may be recommended. Schlesinger gave neutralon 3 times a day before meals, and 0.01—0.02 gramme ( $\frac{1}{6}$ — $\frac{1}{3}$  grain) of extract of belladonna in pills immediately after meals. In order that the treatment may be successful, the medication must be accompanied by a strictly regulated diet. In 51 cases the author was able to watch the course of treatment regularly for a long time. There were 25 cases of hyperchlorhydria, 17 cases of hyper-

\*) Compare Merck's Report 1908.

Schlesinger, Münchener medizinische Wochenschrift 1911, p. 2163.

secretion and 9 cases of gastric ulcer. In 2 cases of gastric ulcer the treatment failed, but neither was treatment by means of bismuth preparations more successful in these cases. Otherwise neutralon only failed in 2 cases, in which, besides the anomalies of secretion, there were marked symptoms of retention which called for regular stomach lavage. Treatment with neutralon extended, on an average, over 4 to 6 weeks until permanent improvement resulted. It then usually remained permanent and only in 2 cases had the cure to be repeated. Kühn, also, is in favour of the employment of neutralon when there is no intestinal lesion and a gradual neutralisation of the gastric acidity is required.

### Nickel Sulphate.

Since Simpson recommended nickel for migraine, the preparation has scarcely been mentioned in therapeutic literature, and its medicinal use has remained restricted. Kolipinski has recently studied the question as to whether the preparation was not deserving of greater interest, and he arrived at most favourable results. According to him, nickel sulphate has a strong antiparasitic action, which makes its external administration most suitable for the treatment of various skin affections. The author used the preparation in the form of 1 to 2 p.c. aqueous solutions for compresses, or applied the lotion to the diseased skin areas and left it to dry. Kolipinski achieved cures by this treatment in impetigo contagiosa, pityriasis circinata, trichophytia and eczema marginatum. In alopecia areata the author even observed a growth of fine new hairs after the expiration of a week, which led in 6 weeks to the normal covering of the scalp with hair. In acne vulgaris, also, the external application of the drug is beneficial, and for pale patients it may with advantage be prescribed internally. Other indications for its internal use are chorea, nervous disturbances accompanied by spasm, chronic facial neuralgia, migraine, chronic enteritis, epilepsy, physical and mental debility and neurasthenia. Doses of 0.03 gramme ( $\frac{1}{2}$  grain) often give good results, but the

Kühn, Fortschritte der Medizin 1911, No. 7.

Simpson, Monthly Journal 1852, No. 8.

Kolipinski, Journal of the American Medical Association 1911, Vol. 57, p. 337. — Monthly Cyclopedic and Medical Bulletin Philadelphia 1911, June.

author considers a normal effective dose to be 0.06 gramme (1 grain). It is given 3 to 4 times a day, preferably after meals. His experiments show that doses of 0.12 to 0.3 gramme (2—5 grains) are rather too large, as they sometimes cause giddiness and vomiting. The drug may be administered in the form of pills, tablets or aqueous solutions. It may be noted that Kolipinski declares cobalt sulphate, which is toxicologically nearly related to nickel sulphate, to be therapeutically inactive.

On the basis of the nickel-biuret reaction described by J. Gnezda, E. H. Fittipaldi has elaborated a method of testing for albumoses in the urine and blood, which distinguishes them with certainty from genuine albuminous bodies. For this purpose the author recommends a mixture of equal parts of a 5 p.c. aqueous solution of nickel sulphate and liquid ammonia, which must always be freshly prepared. In carrying out this test, 10 to 20 c.c. of the urine to be tested are added to 6 times this volume of absolute alcohol and the mixture is put on one side until the following day in order that any albumin which is present may be precipitated. The alcohol is then carefully poured off, the precipitate is dissolved in the least possible quantity of caustic soda solution (31 to 32 p.c. of NaOH) and one drop of the nickel reagent described above is added. If albumoses or peptones are present, a reddish-orange coloration appears immediately, or within a few seconds. The presence of albumoses and peptones are demonstrated together, but this, according to the author, is no great disadvantage as the diagnostic significance of the two substances in the urine is always the same. The advantage of this method over other methods is, that in order to demonstrate the presence of albumoses, the albumins need not first be removed, even if these are present in large quantities.

For the demonstration of albumoses in the blood, 10 to 20 grammes of purified animal charcoal are added to 10 to 20 c.c. of blood; this is well mixed, heated to boiling, allowed to cool and filtered. The filtrate thus obtained is mixed with 6 times its amount of absolute alcohol and the test is proceeded with as described above.

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Gnezda, Proceedings of the Royal Society, London Vol. 47, p. 202.

Fittipaldi, Deutsche medizinische Wochenschrift 1911, p. 1890. —

Riforma medica Vol. 21, No. 35.

**Novoiodin.**

F. R. von Friedländer describes his experiences in the treatment of wounds with this new antiseptic. He used it chiefly in minor surgery and obtained good results. It is non-toxic, hastens the formation of granulations, diminishes the secretion, and rapidly changes the latter into a serous secretion, especially in tuberculous fistulæ. It also has a desiccating, action, without leading to the formation of crusts and hastens the formation of skin over the granulations. In burns of the first degree it hastens the healing process, while in deeper burns the tanning of the healthy skin causes an unpleasant sensation of tauntness. Treatment with novoiodin is, however, suitable for tuberculous fistulæ. For these novoiodin is used either in the form of bougies or of an emulsion.

The preparation is useful, according to Drachter, in surgical tuberculosis, and, according to C. Bohac, in soft sore, suppurating glands, incised buboes, ulcers of the leg and open wounds. Wicherkiewicz has also used it with benefit in ophthalmic practice. As novoiodin, being a mixture of hexamethylenetetramine-di-iodide and talc\*), occasionally caused severe pain, the author later on only used for ophthalmological purposes a mixture of hexamethylenetetramine-di-iodide (10 to 20 p. c.) and milk sugar, which caused neither pain nor irritation. This mixture gave satisfactory results in *ulcus corneæ serpens*, threatening metastatic panophthalmitis after cataract extraction, abscesses of the eyelids, inflammation of the edge of the lid, suppuration of the lachrymal sac, etc. For sensitive patients, 2 p.c. of novocaine may be added to the drug for diseases of the cornea.

**Nucleinic Acid.**

O. Fischer and J. Donath, as is well known, were successful in their treatment of progressive paralysis with

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Friedländer, *Medizinische Klinik* 1911, p. 1458.

Drachter, *Zentralblatt für Chirurgie* 1911, No. 34.

Bohac, *Klinisch-therapeutische Wochenschrift* 1911, p. 747.

Wicherkiewicz, *Heilkunde* 1911, No. 5.

\*) Compare Merck's Report 1910.

Fischer, Merck's Report 1909, p. 88.

Donath, Merck's Report 1910, p. 69.

Donath, *Berliner klinische Wochenschrift* 1910, p. 2343.

injections of sodium nucleinate, a success which makes the further study of treatment with nucleinic acid in this disease desirable. The further experiments of Donath have confirmed the value of nucleinic acid in other cases of initial paralysis, and this is corroborated by Jurmann. The results reported by O. L. Klieneberger were less encouraging. In 15 cases in which the diagnosis of progressive paralysis had been confirmed, the author was unable to detect any noticeable improvement consequent upon injections of nucleinic acid, although some of the patients had gained considerably in weight through treatment at institutions. He even asserts that several of the patients became acutely worse as a consequence of the injections, though this was generally transitory. Besides this, the injections were always accompanied by pain, and almost regularly led to painful infiltrations. Donath believes that these failures were due to the fact that Klieneberger generally tried this method of treatment on somewhat advanced paralytics, while he himself had expressly pointed out that nucleinic acid was only of use in the early stages of the disease. According to him, infiltrations can generally be avoided if the site of injection be changed. Three of his patients, whom he was able to follow up, are fully capable of attending to their business, one of them now for 3 years, although before treatment with nucleinic acid this patient had been quite incapacitated for a considerable time on account of advanced dementia. Fischer, also, recently observed 5 cases of improvement among 10 cases, of whom 3 were again able to attend to their duties. Among 10 control experiments Fischer only once knew an improvement to occur and this was after prolonged suppuration. J. Loewenstein's results appear less favourable as regards the nucleinic acid treatment of paralysis, for among 13 cases not a single one was benefited. In the author's opinion the employment of nucleinic acid brought about neither more instances of improvement or greater benefit than is customarily the case without special treatment. Hussels also perceived

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Jurmann, Russkij Wratsch, 1911, No. 46.

Klieneberger, Berliner klinische Wochenschrift 1911, p. 330.

Donath, Berliner klinische Wochenschrift 1911, p. 555.

Fischer, Medizinische Klinik 1911, p. 321.

Loewenstein, Berliner klinische Wochenschrift 1911, p. 714.

Hussels, Archiv für Psychiatrie, Vol. 48, No. 3.

no special benefit to result from the use of sodium nucleinate in 5 cases of progressive paralysis. In order to explain the action of nucleinic acid in paralysis a work by M. Tshernoruzki may be consulted; he examined the action of nucleinic acid on the fermentative processes in animals and found that after intravenous infusion of sodium nucleinate the proportion of diastase, amylase and protease in the brain of the animals was decidedly increased. He also demonstrated that sodium nucleinate had no harmful influence on the animal organism.

E. von Graff and B. Aschner express their opinions as to the value of nucleinic acid injections before the performance of laparotomy. In over 1000 cases von Graff injected a freshly prepared 2 p.c. solution of sodium nucleinate below the collar-bone on the night preceding the operation; he observed that in gastro-enterostomies, resections of the stomach and bowel and operations on the gall-ducts there was a considerable reduction in the mortality. But he did not consider this success to be solely due to the nucleinic acid injections, but rather to the advances in technique, for those cases of operation not treated by nucleinic acid showed a decided improvement as regards mortality when compared with operations carried out in preceding years. Aschner, also, points out that sodium nucleinate acts better when injected into the peritoneal cavity than when given subcutaneously.

The success of nucleinic acid treatment in multiple sclerosis is noteworthy. S. Bondi reports 11 cases in which he used injections of sodium nucleinate. In 8 cases there was a marked improvement, 3 cases refused further treatment so that no opinion can be expressed, and in only one case no improvement was noticeable after 7 injections.

The use of nucleinic acid injections in rickets finds support in the communication of J. Meisen as to the action of nucleinic acid on the blood and the bone marrow; the author comes to the following general conclusions. Nucleinic acid constantly causes hyperleucocytosis without harmful by-effects. There is no displacement of the neutrophile blood picture to the left in Arneth's sense, e.g., there is no increase

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Tschernoruzki, *Biochemische Zeitschrift* 1911, Vol. 36, p. 363.  
von Graff-Aschner, *Zentralblatt für die gesamte Therapie* 1911, p. 355.

Bondi, *Münchener medizinische Wochenschrift* 1911, p. 2644.  
Meisen, *Medizinische Klinik* 1911, p. 1946.

of the mononuclear neutrophiles. — By constant injections a rise and fall in the number of red blood corpuscles and in the hæmoglobin content is attained. — Nucleinic acid injections, continued for a prolonged period, give rise to greater firmness in bones in the course of development.

### **Omnopon (Pantopon).**

Tomaschny and Oláh report on the employment of omnopon in psychiatry. According to Tomaschny, it has proved useful in mild conditions of excitement and fear, and less useful in melancholia. Oláh, in order to increase the sedative action of the drug, combined it with sodium bromide in the following manner: Rp. Sod. brom. 15.0 grammes ( $\frac{1}{2}$  oz), omnopon 0.15 gramme ( $2\frac{1}{2}$  grains), Aq. destill. 200.0 grammes ( $6\frac{2}{3}$  oz). Of this mixture 1 tablespoonful is given 3 to 4 times a day. For insomnia he prescribed omnopon internally in tablets, and subcutaneously according to the formula: Morph. hydrochl. 0.005 to 0.01 gramme ( $\frac{1}{12}$ — $\frac{1}{6}$  grain), omnopon 0.01 to 0.02 gramme ( $\frac{1}{6}$ — $\frac{1}{3}$  grain); or Hyoscin. hydrobrom. 0.0005 to 0.001 gramme ( $\frac{1}{125}$ — $\frac{1}{64}$  grain), omnopon 0.01 to 0.02 gramme ( $\frac{1}{6}$ — $\frac{1}{3}$  grain) per dose. This medication is also said to develop a satisfactory hypnotic action in the more severe irritative conditions of the psycho-motor system.

Taken internally omnopon, like opium, acts as a sedative on the intestine, and this has recently been confirmed by Nürenberg, K. Mitterer and A. Döblin; for this reason F. Zollinger prescribed it for the alleviation of the profuse diarrhoea of typhoid. 3 daily doses of 0.01 gramme ( $\frac{1}{6}$  grain) are said to have had a good effect. The author employed it subcutaneously for patients suffering from typhoid fever to facilitate their removal to an hospital; a dose of 0.02 gramme ( $\frac{1}{3}$  grain) of omnopon made it possible to prevent defæcation during the transport and thus to protect the transport apparatus from being soiled.

As omnopon increases gastric secretion and would thus appear to be contra-indicated in gastric ulcer, Rodari com-

Tomaschny, *Neurologisches Zentralblatt* 1911, No. 3.

Olah, *Gyogyaszat* 1911, No. 17.

Nürenberg, *Ruskij Wratsch* 1911, p. 190.

Mitterer, *Therapie der Gegenwart* 1911, p. 383.

Döblin, *Therapeutische Monatshefte* 1911, p. 216.

Zollinger, *Korrespondenzblatt für Schweizer Ärzte* 1911, No. 10.

Rodari, *Schweizer Rundschau für Medizin* 1911, p. 105.

bines it with atropine in order to get rid of this troublesome by-effect. He obtained good results with the following formula: Rp. Atropin. sulph. 0.01 gramme ( $\frac{1}{6}$  grain), omnopon 0.2 gramme (3 grains), Aq. laurocer. 10.0 grammes ( $\frac{1}{3}$  oz); 10 to 15 drops of which were taken 2 to 3 times.

O. Dornblüth, in his experiments with omnopon, made the observation that after having administered large doses it was perfectly easy to withhold the drug. He therefore suggests replacing morphine by omnopon in the treatment of morphinism. It is said that on withholding the omnopon, no craving for morphine occurs.

In employing omnopon in the induction of anæsthesia before operations, C. L. Leipoldt states that in his experience omnopon injections are more effectual than a combination of omnopon and scopolamine\*), as it gives rise to neither nausea nor vomiting. It may therefore be used in valvular disease and icterus, and for children. The only secondary effects observed by the author were intense thirst and greatly increased secretion of sweat. On the appearance of toxic symptoms he recommends injections of potassium permanganate solution. J. Voigt reports a case of poisoning by omnopon following 2 injections, each of 0.02 gramme ( $\frac{1}{3}$  grain) of omnopon. This case proves that in the presence of idiosyncrasy, omnopon may also give rise to symptoms of intoxication.

## Organotherapeutic Preparations.

### Hormonal.

The peristaltic hormone, the so-called hormonal, which was introduced into therapeutics by Zuelzer, was discussed last year by Unger, Strauss, Plehn, Zuelzer, Kauert,

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Dornblüth, Deutsche medizinische Wochenschrift 1911 p. 697.

Leipoldt, Lancet, 1911, I, p. 368.

\*) Compare the article on "Scopolamine".

Voigt, Therapeutische Monatshefte 1911, p. 601.

Zuelzer, Therapie der Gegenwart 1911, p. 197.

Unger, Strauß, Plehn, Zuelzer, Berliner klinische Wochenschrift 1911, p. 495.

Kauert, Münchener medizinische Wochenschrift 1911, p. 907.

Glitsch, Forkel, Lenormant, Pfannmüller, Dittler, Jacoby and Mächtle\*).

From the communications of these authors, it may be seen that hormonal is a useful drug in various forms of constipation. But as the results were negative in a number of cases, an attempt has been made to determine the indications as definitely as possible. Pfannmüller is most definite on the subject and he gives the results of his investigations as follows: Hormonal yields good results in hypotony and atony of the intestines, e. g., in chronic habitual constipation, the atonic form and milder mixed forms of spastic-atonie constipation — post-operative obstruction. Atony of the ampulla forms an exception. On the other hand, no benefit can be expected in spastic constipation in a limited sense, in severe chronic constipation of the ampulla and in constipation due to any mechanical cause (peritoneal adhesions, retroflexed adherent uterus, hypertrophy of the prostate, etc.).

The dosage varies, according to the severity of the case, from 20 to 40 c.c., which amount was usually tolerated without marked by-effects, but which often required supplementary treatment with internal aperients (castor oil) or with enemata. But occasionally pain, fever and rigors were observed to follow the injection of hormonal. Dittler further reports on the action of the drug in lowering the blood pressure, which in one case, after intravenous injection, led to dangerous collapse. Possibly on this account intra-gluteal injections will be preferred as, according to Kauert, they have the same effect as its intravenous application.

The time of commencement of the action appears to vary considerably. It is said usually to occur in the course of 2 to 26 hours, but in some cases it does not occur for 3 days.

### Liver.

While Gilbert and Carnot recommended the use of liver in the treatment of the hæmoptysis of tuberculosis, H.

Glitsch, Münchener medizinische Wochenschrift 1911, p. 1243.

Forkel, Münchener medizinische Wochenschrift 1911, p. 1875.

Lenormant, Presse médicale 1911, p. 755.

Pfannmüller, Münchener medizinische Wochenschrift 1911 p. 2270.

Dittler-Mohr, Münchener medizinische Wochenschrift 1911, p. 2427.

Jacoby, Deutsche medizinische Wochenschrift 1911, p. 2125.

Mächtle, Therapeutische Monatshefte 1911 p. 652.

\*) Compare Merck's Report 1910, p. 271.

Gilbert-Carnot, Gazette des hôpitaux 1900, p. 995. — Compare Merck's Report 1908, p. 58.

Parmentier considers that liver medication has in general a favourable influence on tuberculosis. According to him, it brings about an increase in weight, a decrease in the night sweats and finally the disappearance of tubercle bacilli. The author was able to confirm its beneficial effect on hæmoptysis. The action of liver is thought not to be due to a definite substance, but rather to the combined action of all the active substances contained in the liver, for which reason Parmentier used an extract of liver (so-called cholergin). It is prepared from ox liver and gall and is injected subcutaneously in sterilised oily solution daily or on alternate days. The treatment is indicated in commencing tuberculosis, curable manifest tuberculosis and bronchitis, and an improvement is said to be apparent in the majority of cases after about 30 injections. It is said that it is never contra-indicated and that it may even be employed in febrile cases. The author draws special attention to a case of tuberculosis of the testicle, in which the injections proved successful, but he also hopes for good results in other infections, such as hepatic insufficiency and the gastro-enteritis of young babies.

### Mammary Gland Substance.

R. Bell is well known to have been the first to point out the value of mammary gland therapy in uterine fibroma and hæmorrhage from the uterus, a measure which was later recognised to be very useful by various investigators, including Shoher, Pryor, Crouse, Fedoroff, Kalabin, Sellheim, Mekertschiantz, Goldmann, Batuaud, Hallion and Carrion, Dalché, and others. J. Luncz has also recently published the results of his investigations on this subject. He used an extract of the mammary gland, 1 gramme of which corresponded to 7 grammes of the fresh organ; of this he gave 0.5 gramme twice a day. This amount corresponds to about 0.4 gramme of *mammæ siccatae* or 4 tablets (*mammæ siccatae*, compressed tablets of 0.1 gramme). The drug is best given before the two principal meals and the treatment must be stopped immediately on the appearance of gastric disturbances. In uterine

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Parmentier, *Bulletin général de thérapeutique* 1911, No. 6.

Bell, *Merck's Report* 1908, p. 71. (*Medical Times and Hospital Gazette* 1897, No. 1008.)

Luncz, *Revue de thérapeutique* 1911, No. 15, p. 505. — *Revista de medicina y cirugía* 1911, No. 8.

fibroma it is necessary, in order to bring about the disappearance of the tumour, to continue the treatment without interruption for months, and this is easy as the use of the preparation is free from danger. The hæmorrhage occurring with uterine fibroma is benefited to a marked degree so that occasionally an operation which seemed necessary can be dispensed with. If, however, an operation is necessary, it takes a more favourable course under the influence of mammary gland substance than without it. But if an operative procedure is contra-indicated on account of cardiac, pulmonary or renal complications, organotherapy represents the only safe treatment which can be employed. This medication has also proved valuable in the menorrhagia of young girls, and in the metrorrhagia of the climacteric.

### Ovaries.

According to R. Einhauser, ovarian therapy\*) will always lead to relief of pathological symptoms in functional disturbances of the ovary, if the administration of ovarian substance be indicated and if a good ovarian preparation be used which contains the active substances of the ovary in an unaltered form. The greatest difficulty, however, appears to lie in a correct determination of the indications, as symptoms are often absent or have no connection with the functional disturbance of the ovaries or with their operative removal and were perhaps present before the operation, without having been noticed by the patients on account of the pains which were present. It goes without saying that an absolutely reliable preparation must be made use of for organotherapy. For it is well known that some organ preparations completely lose their action if not treated and dried with sufficient care. But this is not the case with all substances obtained from animal organs now on the market, and is probably only partially true of ovarian substance. As is shown in a paper by G. Schickele, this substance is sensitive to heat but not to alkalis, for on coming into contact with alkalis or when neutralised by them, it loses its action. More exact knowledge will be gained on the subject when the active substance or substances of the ovaries have been isolated

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Einhauser, Münchener medizinische Wochenschrift 1911, p. 355.

\*) Compare Merck's Report 1908, p. 77.

Schickele, Münchener medizinische Wochenschrift 1911 p. 123.

and identified, which has not as yet been done. Schickele considers the active principle of the ovary to be a substance which in vitro exhibits a powerful action tending to diminish coagulability of the blood. He found, besides, that the intravenous application of this substance gives rise to marked lowering of the blood pressure, due to dilatation of the blood vessels and often accompanied by a definite delay in the coagulability of the body blood; this causes the appearance of convulsions and spasms with partial numbness, retardation of the respiration and the pulse, and sometimes contractions of the bowel. It is known that an action of lowering the blood pressure is also attributed to choline, but the ovarian action can scarcely be due to this body, as the ovarian action is much more intense and is not arrested by atropine, as is the case with choline. Nor has Schickele been able to demonstrate chemically the presence of choline in the fluid expressed from the ovaries.

The significance of ovarian therapy is dealt with by H. Offergeld, R. Kahane and H. Walther. Offergeld used for his experiments ovaraden and ovaraden-triferrin\*). He obtained good results with them in chlorosis and in the accompanying symptoms in the genital organ, in sudden cessation of the menses consequent upon cold, fright, altered mode of living, etc., in secondary anæmia consequent upon persistent hæmorrhage in abortion and atrophy of lactation, in disturbances of the vasomotor system, etc.

Kahane recommends ovaraden-triferrin in daily doses of 2 tablets in all cases of natural and artificial climacteric, in chlorosis and in functional disturbances of the ovaries. In delayed menstruation the menses returned practically to normal, in climax præcox the troubles disappeared after taking only a few tablets, and in a case of natural climacteric the tumultuous symptoms could be considered cured after the administration of 50 tablets. Walther also prescribed ovaraden-triferrin with good results in natural and artificial climacteric, in the amenorrhœa and dysmenorrhœa of youth and in menstrual disturbances after post-puerperal inflammation of the pelvic connective tissue, the adnexa and the perimetrium.

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Offergeld, Deutsche medizinische Wochenschrift 1911, p. 1172.

Kahane, Heilkunde 1911, No. 12.

Walther, Münchener medizinische Wochenschrift 1911, p. 2562.

\*) Merck's Report 1909, p. 276.

A. Kuhn now obtained such good results by the use of ovaraden-triferrin in sexual neurasthenia with frigidity that he places the preparation in the group of the aphrodisiacs.

### Pituitary Body.

In the case of several children with arrested development of the brain Bahrman used hypophysis tablets\*) with good results, and in the same way he used hypophysochrom tablets\*\*) in 2 patients with early menopause, who were suffering from a condition of sexual excitement and insomnia. The results were satisfactory in every case.

Recently, extracts have been prepared from the pituitary body which contain the active substance of the gland; they can be administered subcutaneously and thus render the treatment more reliable. The best known are pituitrin, pituglandol and vaporole. As the method of preparation of these products is not exactly known, their composition cannot be described, but probably they do not differ from one another to any great extent. Vaporole was used by Ross with good result to stimulate labour pains, and it thus corresponds in action to pituitrin (Compare the article on "Pituitrin" below). Voigts states that pituglandol has the same action.

### Pituitrin.

Pituitrin is an extract of animal hypophysis, and is prepared from the posterior lobe of the pituitary body, as the substances in the anterior lobe give rise to different physiological and pharmacological effects. Thus, in the liquid form in which it is put on the market, it consists of a (colourless) solution of the active substance or substances of the infundibular portion of the pituitary body. The active substance has not as yet been minutely investigated and it cannot therefore be chemically identified. All that is known so far is that its action is similar to that of adrenalin; but it cannot be chemically identical with it, as it does not give the well known adrenalin reactions. Possibly it contains a substance which,

Kuhn now, *Frauenarzt* 1911, No. 10.

Bahrman, *Medizinische Klinik* 1911, p. 223.

\*) Compare Merck's Report 1908, p. 62.

\*\*) Compare the article on "Adrenochrom" in Merck's Report 1910.

Ross, *Zentralblatt für Gynäkologie* 1911, No. 34.

Voigts, *Deutsche medizinische Wochenschrift* 1911, p. 2237.

like adrenalin, possesses an alkylised amino-nitrogen\*). As regards the relationship of pituitrin to the substance from which it is obtained, 1 c.c. of pituitrin is said to correspond to 0.2 gramme of fresh pituitary substance.

The results of pharmacological and clinical experiments have been described by Dale, Frankl-Hochwart, Franchini, Blair Bell, Foges and Hofstätter, Bondy, Bagger-Jørgensen, Gottfried, Fries, Krömer, Pfeifer, Neu, Aarons, Hofbauer, Vogt, Klotz, Hofstätter, Bab, Stern, Stiassny, Marek, Schmid, Schiffmann, Jacobi, Steuernagel, Falta and Fleming, Hell, Voigts, Hahl, Cahn and Kehrер.

\*) Compare Allers, Münchener medizinische Wochenschrift 1909, p. 1474.

Dale, Journal of Physiology Vol. 24, No. 3.

Frankl-Hochwart, Archiv für experimentelle Pathologie Vol. 63, p. 347. — Merck's Report 1910, p. 269.

Franchini, Berliner klinische Wochenschrift 1909, p. 613.

Bell, British Medical Journal 1909, II, p. 1409 and 1609.

Foges-Hofstätter, Zentralblatt für Gynäkologie 1910, No. 46.

Bondy, Berliner klinische Wochenschrift 1911, p. 1461.

Bagger-Jørgensen, Zentralblatt für Gynäkologie 1911, No. 37.

Gottfried, Zentralblatt für Gynäkologie 1911, No. 14.

Fries, Münchener medizinische Wochenschrift 1911, p. 2438.

Krömer, Zentralblatt für Gynäkologie 1911, No. 39.

Pfeifer, Zentralblatt für Gynäkologie 1911, No. 22.

Neu, Zentralblatt für Gynäkologie 1911, No. 35.

Aarons, Klinisch-therapeutische Wochenschrift 1911, p. 332.

Hofbauer, Zentralblatt für Gynäkologie 1911, No. 4. — Monats-schrift für Geburtshilfe und Gynäkologie 1911, No. 3.

Vogt, Münchener medizinische Wochenschrift 1911, p. 2743.

Klotz, Münchener medizinische Wochenschrift 1911, p. 1119.

Hofstätter, Wiener klinische Wochenschrift 1911, p. 1702.

Bab, Münchener medizinische Wochenschrift 1911, p. 1554.

Stern, Berliner klinische Wochenschrift 1911, p. 1459.

Stiassny, Gynäkologische Rundschau 1911, No. 13.

Marek, Wiener medizinische Wochenschrift 1911, No. 34.

Schmid, Gynäkologische Rundschau 1911, No. 15.

Schiffmann, Klinisch-therapeutische Wochenschrift 1911, p. 1498.

Jacobi, Deutsche medizinische Wochenschrift 1911, p. 2125.

Steuernagel, Medizinische Klinik 1911, p. 1836.

Falta-Fleming, Münchener medizinische Wochenschrift 1911, p. 2649.

Hell, Münchener medizinische Wochenschrift 1911, p. 2651.

Voigts, Deutsche medizinische Wochenschrift 1911, p. 2286.

Hahl, Finska Läkaresällskapets Handlingar 1911, 11<sup>th</sup> October.

Cahn, Dissertation, Freiburg i. Br. 1911.

Kehrер, communicated by Vogt.

After the action of pituitrin in causing uterine contraction had been confirmed by Frankl-Hochwart and Dale, and the preparation had been used with benefit by Foges and Hofstätter in post-partum hæmorrhage, many of the above named authors paid special attention to its action on labour pains. Hofbauer found that the subcutaneous application of 0.6 to 1.2 gramme of pituitrin gave rise to regular labour pains and that in the period of expulsion its action was occasionally most striking. As it causes no troublesome by-effects, and none of a tetanic nature, the experiences of the above named authors regarding the value of pituitrin in feeble pains are almost entirely satisfactory. According to Vogt, the preparation acts with promptitude and certainty in the expulsive period. It serves to hasten normal delivery and, as Kehrer pointed out at the Gynæcological Congress in Munich, it is useful in the treatment of secondary inertia, even with a contracted pelvis. The action is most effective in the expulsive stage, and appears to be less constant in the first stage. On the other hand, its action after the expulsion of the placenta is not as yet exactly known, and Zangemeister does not use the preparation after the third stage. Steuernagel considers nephritis and myocarditis to be contra-indications. Pfeiffer and Gottfried alone have reported failures after pituitrin administration.

Pituitrin also appears to play an important part in post-partum hæmorrhage. Klotz confirms the statements of Foges and Hofstätter on this point. In his experience, pituitrin is a substance which gives rise to a moderate rise in blood pressure persisting for hours and with only a slight demand on the heart. It also increases the strength of the heart, stimulates intestinal peristalsis, increases the excretion of urine and stimulates the action of the bladder. Evidence is thus given of a number of new indications, which are of interest with regard to pituitrin and which will occupy clinicians in the future. Thus Hofstätter has used the preparation with good results as a bladder tonic. Neu further reports on the utility of the drug in osteomalacia. With intramuscular injections of 0.5 to 1 c. c. he effected a considerable improvement in a multipara aged 35.

With regard to the form of administration, according to present experience, intramuscular and intravenous application

of pituitrin appears to offer the greatest advantages. The most favourite method appears to be that of intramuscular injection, but as regards persistence and intensity of action it is said not to correspond entirely with the intravenous application. The maximum dose has not yet been settled; 1 c.c. may at present be considered a normal dose for an adult.

### Spleen.

Bayle, who once before reported on the strikingly good results of the use of spleen in tuberculosis, has recently again pointed out the advantages of this treatment. In a large number of cases (pulmonary tuberculosis and surgical tuberculosis) he administered 100 grammes a day of fresh pig's spleen (corresponding to 20 grammes of *lien siccatus*) in lukewarm broth or in jam. The medication was carried out in series each lasting for 3 weeks, with intervals of 2 weeks. It is generally very well tolerated, but if this should not be the case an extract of spleen of good quality may be injected locally. The author states that he brought about a cure in 75 p.c. of his cases of pulmonary tuberculosis, some of which were far advanced. Various cases of tuberculous adenitis, bone tuberculosis and coxalgia were cured without a single exception. Joly also confirms the value of spleen medication, which he considers to have a specific action. Local tuberculosis is said to be healed ten times more rapidly than when the usual classical forms of treatment are employed alone.

### Thyroid Gland. (Thyroidin.)

The value of thyroid gland in the treatment of obesity is dealt with in a paper by C. Pariser and P. E. Richter. In endogenous obesity the only correct treatment, according to Pariser, is an etiological one, e. g., the administration of thyroid gland. For the first 3 to 4 days 1 to 2 thyroid gland

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Bayle, *Revue internationale de médecine* 1908, p. 241. — Merck's Report 1908, p. 67.

Bayle, *Revue de médecine* 1911, No. 6. — *Deutsche Medizinalzeitung* 1911, p. 903.

Joly, communicated by Bayle.

Pariser, *Zeitschrift für ärztliche Fortbildung* 1911, No. 3. — *Deutsche Medizinalzeitung* 1911, No. 25.

Richter, *Medizinische Reform* 1911, No. 5. — *Therapeutische Monatshefte* 1911, No. 5.

tablets Merck are taken, the dose is then increased to 3 tablets for 8 to 10 days and in exceptional cases to 4 tablets; during the next 8 days 2 tablets are taken, then 1 tablet for 5 to 8 days, after which the medication is left off entirely for a week. This interval is left on account of the cumulative action of thyroid and serves to allow the secondary effects of the drug to wear off gradually. For the same reason, after this treatment has been repeated twice or three times, a longer interval of about 3 months may be allowed to elapse. This is regulated according to the patient's loss of weight, which must always be kept under control. The surest sign of the commencement of cumulative action is an increase in the pulse rate. If this rises to 100—110 the use of the drug must be discontinued and rest prescribed. If in the course of 3 to 4 days the pulse has returned to normal, the administration of the drug may be resumed. The diet naturally plays an important part in cures for obesity. It should be not too poor in carbohydrates, rich in albumin, but poor in fats. Richter also expresses a similar opinion.

The thyroid treatment of carcinoma deserves consideration. E. Hughes Jones, in a case of multiple carcinoma of the skin and subcutaneous tissue, effected a considerable improvement in the general health and disappearance of the growths by the administration of 0.32 to 1.0 gramme (5—15 grains) of thyroid extract. He therefore recommends the use of the preparation in inoperable carcinomata or in cases in which operation is refused, and also as a supplementary treatment after operation, and to prevent recurrences. In inoperable carcinoma of the breast occurring before the menopause, oöphorectomy is recommended, combined with the administration of thyroid gland; during the climacteric this operation is said to be useless. But oöphorectomy is, in the author's opinion, less effective in the former case than thyroid treatment. In the presence of visceral metastases, however, nothing can be expected from it. The author assumes that thyroid acts as follows: the drug increases albumin metabolism and thus curtails the life of the carcinoma cell, and, further, by encouraging the formation of fibrous connective tissue cells, withdraws from the carcinoma cell the substratum favourable for its development. Good results obtained by the thyroid gland

treatment of carcinoma are reported by Diesing, who also uses an extract of the thyroid gland. A successful effect was apparent in gastric carcinoma, whether the drug was exhibited internally or intramuscularly, the latter method proving specially suitable in the presence of vomiting. The favourable reports of these two authors justify further tests of their method of treatment in suitable cases. Diesing, for his tests, used the so-called "thyrochrom", an ethereal-alcoholic extract of the thyroid gland of sheep and calves.

A. E. Hodgson has used thyroid with good results in the treatment of serum disease. In 50 cases, simultaneously with, or after the injection of diphtheria serum, he gave 0.075—0.3 gramme ( $1\frac{1}{6}$ —5 grains) of thyroid gland a day, according to the age of the child, in 4 to 6 single doses. At the same time he kept under observation an equal number of cases in which thyroid had not been used. The result of this investigation showed that thyroid gland substance is capable of restricting the appearance of symptoms of serum disease.

Reference may be made to the communications of P. Mathes on the acceleration of the coagulation of the blood by thyroid gland juice; of Marbé on the increase in the secretion of gastric juice by feeding with thyroid gland; and especially of L. Haskovec, on the action of thyroid extract. These communications do not lend themselves to abstraction.

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### **Peganum Harmala.**

The aqueous extract of the roots of *Peganum Harmala* L., when injected subcutaneously, has, according to W. Schindler, a purgative action. But, as in the animals used for experiment (dogs), indurations resulted at the site of injection, some of which remained indolent, while others suppurated after 3 to 4 weeks, it is improbable that harmala extract will be used subcutaneously in human beings. It has not as yet been discovered which component of the harmala plant possesses the eccoprotic action.

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Diesing, *Medizinische Klinik* 1911, p. 458.

Hodgson, *Lancet* 1911, 11<sup>th</sup> February p. 373.

Mathes, *Münchener medizinische Wochenschrift* 1911, p. 1003.

Marbé, *Semaine médicale* 1911, p. 322.

Haskovec, *Wiener klinische Wochenschrift* 1911, p. 1117.

Schindler, *Petersburger medizinische Wochenschrift* 1911, p. 135.

*Peganum harmala* is a shrub-like growth, widely distributed in the Southern Steppes, which has only been used as a popular remedy. In the Orient especially, the seeds are said to have been used as a popular remedy in diseases of the eyes, and also as a diaphoretic, anthelmintic and an intoxicant (like hashish), and the leaves for compresses and baths. Technically the plant has been found of use as a dye. In their investigation of the plant, Göbel, Fritzsche and Fischer found two bodies, harmin and harmalin.

Harmin,  $C_{13}H_{12}N_2O$ , is a mono-acid secondary base, melting at  $257^{\circ}C$ . the salts of which show in aqueous solution a strong blue fluorescence.

Harmalin,  $C_{13}H_{14}N_2O$ , (also called dihydro-harmin) is a mono-acid secondary base, melting at  $238.5^{\circ}C$ ., the salts of which show a yellowish-green fluorescence in aqueous solution. By oxidation it can be converted in harmin, which by further oxidation gives harminic acid,  $C_{10}H_8O_4N_2$ , (with an indefinite melting point above  $250^{\circ}C$ .). On heating this breaks down into apoharmin,  $C_8H_8O_2$ , an unsaturated secondary base melting at  $186^{\circ}C$ . On reduction harmin and harmalin form tetrahydroharmin (identical with dihydroharmalin).

Communications on the pharmacological action of harmin and harmalin have been made by Penzoldt, H. Tappeiner, A. Neuner and Flury. Penzoldt found that harmin had an antipyretic action, while Tappeiner and Neuner declared harmin and harmalin to be convulsive poisons and also respiratory poisons in that they may cause death by respiratory paralysis. This was confirmed by Flury, who investigated the action of harmin, harmalin, tetrahydroharmin and apoharmin on frogs and warm-blooded animals. The 3 first named substances, according to him, have a directly paralyzing action on frogs, while apoharmin causes an in-

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Göbel, Liebigs Annalen der Chemie und Pharmazie 1841, Vol. 38, p. 363 and Vol. 39, p. 289.

Fritzsche, Journal für praktische Chemie (1<sup>st</sup> Series), Vol. 42, p. 144 and Vol. 44, p. 370.

Fischer, Berichte der deutschen chem. Gesellschaft Berlin 1885, Vol. 18, p. 400, 1889, Vol. 22, p. 637, 1897, Vol. 30, p. 2481.

Penzoldt, Chemische Studien über die Alkaloide der Steppenraute. O. Fischer, Festschrift, Erlangen 1901. (A. Deichert, Leipzig.)

Tappeiner-Neuner, Archiv für experimentelle Pathologie 1895, Vol. 35, p. 69.

Flury, Archiv für experimentelle Pathologie 1911, Vol. 64, p. 105.

crease in reflex excitability. Harmin and harmalin have a paralysing action on the skeletal and cardiac muscles of the frog. Harmalin possesses an anthelmintic action, which may conceivably be due to paralysis of the musculature of the parasite. In warm-blooded animals harmin and harmalin cause tonic-clonic convulsions, great increase in the secretion of saliva, respiratory disturbances and a depression of the temperature of the body, and during the convulsions an increase in blood pressure. After harmalin poisoning in dogs psychic disturbances become manifest of the same kind as produced by cannabinol, and these give experimental pharmacological support to the Oriental custom of using harmala seeds for producing stupefaction and intoxication. The author found that dogs and rabbits became accustomed to large, more than fatal doses of harmin and harmalin, and he considered this to be due to an increasing destruction of the poison in the organism. He considers the seat of destruction to be the blood, liver and nervous tissue, and the products of decomposition to be harmin, harmalol, harminic acid, a nitrogenous acid without known chemical characteristics, and a red colouring matter of unknown constitution.

### Perhydrol.

A communication by Ph. Escherich encourages the use of perhydrol in impetigo and folliculitis. A child, which had suffered from pneumonia and had been treated by the application of moist, warm compresses to the thorax, developed large patches of impetigo and folliculitis in this area after the subsidence of the pneumonia. The author had the affected areas cleansed by soap spirit, the small furuncles opened by means of Cowper's scissors and thoroughly swabbed and cleared out by means of small rods dipped in perhydrol. After a warm corrosive sublimate bath, compresses wrung out of a 3 p.c. perhydrol solution were applied. In 3 days the child was almost cured. Perhydrol is also of value in pruritus occurring in severe icterus; von Hynek obtained good results by the use of a 5 to 8 p.c. solution of hydrogen peroxide applied in the form of a spray. The author reports

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Escherich, Wiener medizinische Wochenschrift 1911, No. 5. —  
Münchener medizinische Wochenschrift 1911, p. 228. — Thera-  
peutische Monatshefte 1911, p. 260.

Hynek, Münchener medizinische Wochenschrift 1911, p. 1431.

a case in which all sedative ointments, spirituous lotions and narcotics had failed. In this case the sprays mentioned above always procured 4 hours of peaceful sleep.

J. Zilz used a 5 p.c. perhydrol solution in osteomyelitis of the jaw for syringing out the cavity laid open by operation. The formation of perhydrol froth forced out the little splinters of bone which had remained behind. The author also describes a case of genuine gonorrhœal stomatitis, in which hourly rinsing of the mouth with a warm 5 p.c. perhydrol solution proved of special value.

Neuber uses perhydrol for the purpose of arresting parenchymatous hæmorrhage after surgical operations. Before the wound is closed, he directs on to it a spray apparatus driven by compressed air and filled with a 3 p.c. perhydrol solution, until the wound is entirely filled with froth. The wound is then firmly stitched up and a tight bandage applied. Almost without exception the wounds heal by first intention.

For the care of the mouth and teeth perhydrol will remain the solution of hydrogen peroxide of choice on account of its absolute purity and freedom from acid. It will in general be preferred to other  $H_2O_2$  preparations in cases in which the  $H_2O_2$  is to come into contact with mucous membranes. This is very evident from the publications of Ch. Greve, H. Seidel, P. Rosenthal, J. B. Viliesid, Ruttloff, A. Fuchs, A. Lichtwitz, Linkersdorff and E. Maddox. Perhydrol is certainly vastly superior in these cases to the so-called stable hydrogen peroxide preparations. Thus Greve has recently declined to use pergenol\*), to which others have attributed all the good qualities of hydrogen peroxide, as his experience is opposed to this statement, although

Zilz, Österreichisch-ungarische Vierteljahresschrift für Zahnheilkunde 1911, No. 1. and 2.

Neuber, Zentralblatt für Chirurgie 1911, No. 36.

Greve, Ergebnisse der gesamten Zahnheilkunde, Vol. 1, No. 4.

Seidel, Zahnärztliche Rundschau 1911, No. 42.

Rosenthal, Journal dentaire belge 1911, July. — Le laboratoire et le progrès dentaire réunis 1910, No. 39.

Viliesid, La Odontologia 1911, No. 3.

Ruttloff, Deutsche zahnärztliche Zeitung 1911, No. 21 and 25.

Fuchs, Zahntechnische Wochenschau 1911, No. 8.

Lichtwitz, Deutsche Monatsschrift für Zahnheilkunde 1911, No. 1.

Linkersdorff, Pharmazeutische Zeitung 1911, No. 69.

Maddox, The Ophthalmoscope 1911, February.

\*) Compare Merck's Reports 1909 and 1910.

he at first expressed a favourable opinion regarding this preparation. He now refers his former favourable criticism solely to the convenient form of pergenol, as he was unable to obtain by its use the beneficial and energetic action of hydrogen peroxide, especially in inflammatory conditions. This can easily be understood from his statement, for each pergenol tablet only corresponds to 0.01 gramme of  $H_2O_2$ , which in the majority of cases is insufficient.

In comparing pergenol and perhydrol Seidel comes to the following impartial conclusion: The preparation of a solution of  $H_2O_2$  can be carried out more conveniently and rapidly in the consulting room by using perhydrol. The solution also keeps better than that prepared with pergenol. As dentists generally use hydrogen peroxide in 3 p. c. solution, which is most effective and at the same time harmless, pergenol, if used in this concentration would contain an unpleasantly high percentage of boric acid. Therefore, for the preparation of 3 p. c. and more concentrated solutions of  $H_2O_2$ , perhydrol alone can be employed. Solutions of this concentration have, in cases of infection, been shown to have the remarkable curative and surprising analgesic action of  $H_2O_2$ . Another point is that the taste of pergenol is more unpleasant to many patients than that of perhydrol.

The great advantage which perhydrol possesses over other hydrogen peroxide preparations, namely its absolute purity, is also emphasised by Lichtwitz. He does not consider it justifiable to substitute other preparations for perhydrol. He gives special instructions for the employment of perhydrol in dental extractions, fillings, pyorrhœa alveolaris, gingivitis, treatment of the roots and dentine anæsthesia. After dental extractions, bleeding is rapidly checked by syringing out the wound with perhydrol (2 to 3 drops) or by the introduction of a tampon dipped in perhydrol; even in suppurating wounds pure perhydrol is said to be beneficial. By using perhydrol, together with rinsing with water, the long wait for the cessation of the hæmorrhage is abolished, which is a matter of importance to both the patient and the doctor. The hæmostatic action of perhydrol is also useful in pulp-extractions, for on account of the rapid cessation of bleeding, the root canal can always be filled at the first sitting. The excellent action of perhydrol in pyorrhœa alveolaris, according to Lichtwitz, depends upon the mechanical as well as upon the antiseptic

properties of perhydrol. He always used it pure, as it froths more when applied in concentrated form, and his results were very good. In gingivitis he prescribed it as a mouth wash (1 + 2 water) containing 10 p.c. of  $H_2O_2$ , as an auxiliary to other forms of treatment. It is of marked assistance in these cases in hastening the process of healing.

According to Linckersdorff, perhydrol is at present the best antiseptic for the mouth, for it fulfils the necessary condition for this purpose, viz., freedom from acids, such as boric acid, lactic acid, salicylic acid, etc. He gives the following prescriptions for the preparation of a mouth-wash:

Rp. Solutio hydrogen. perox. 3 p.c. e perhydrol Merck parat. 250.0 grammes ( $8\frac{1}{3}$  oz), Ol. menth. pip. gtt. l, Ponceau RR 0.01 gramme ( $\frac{1}{6}$  grain).

Rp. Vanillin. 0.25 gramme (4 grains), Saccharin. 0.25 gramme (4 grains), Salol 9.5 grammes (143 grains), Menthol 15.0 grammes ( $\frac{1}{2}$  oz), Tinct. Cocci 25.0 grammes ( $\frac{5}{6}$  oz), Spirit. 850.0 grammes (33 oz), Perhydrol 100.0 grammes ( $3\frac{1}{3}$  oz).

The perhydrol mouth wash of Krewel is perhaps even better than these mixtures and gives the best possible guarantee of keeping well.

An advance has also been made in the process of bleaching the teeth with the help of perhydrol and light. According to Ruttloff and Rosenthal, artificial (electric) light and suitable apparatus are now used in place of sunlight, and thus the process of bleaching is no longer dependent upon the presence of sunlight. According to Ruttloff, treatment by means of Zeiss' apparatus for illuminating the mouth in conjunction with chemically pure perhydrol of high percentage makes it possible to remove completely in a few sittings disfiguring discolorations of the teeth which have persisted for years, in such a way that the bleached tooth will pass without comment among the other teeth. In totally discoloured teeth this object is most rapidly gained by first treating the root and then treating the tooth both externally and internally with perhydrol and white light, whereas in dealing with living teeth dilute perhydrol and blue light are more reliable. Of course, the process of bleaching is only successful if the discoloration of the teeth be due to organic infiltrations, and not if due to inorganic discoloration by copper or mercury. Thus, by means of a combination of perhydrol and light,

the dentist is enabled to remove, without ill effects, pathological discolorations of living and dead teeth.

Fuchs carried out careful experiments to find whether perhydrol exerted any harmful influence upon dental fillings, but his results showed that even the prolonged employment of a 3 p.c. perhydrol solution had not the slightest effect upon the most varied fillings, such as gold, silver, copper, amalgam and cement. In filled teeth, which were left for a fortnight in a 3 p.c. perhydrol solution, there was not a sign of decalcification, while ordinary commercial solution of hydrogen peroxide caused a distinct decalcification of the teeth in this time.

In the extensive employment of solution of hydrogen peroxide for the care of the mouth, no harmful secondary effects have as yet been observed. It cannot be said that the influence, experimentally demonstrated by L. E. Walbum, of  $H_2O_2$  on the enzyme-producing power of the buccal mucous membrane has been practically confirmed. Nor was A. Marcuse, who repeated Walbum's experiments, able to confirm his results, and A. Bickel has expressed the opinion that hydrogen peroxide, used in the concentrations necessary for buccal disinfection, has no deleterious action.

Maddox treats stenosis of the lachrymal duct with dilute perhydrol solution after it has been surgically divided, and then fills the sac with metallic mercury, which causes dilatation of the contracted canal. He repeats the filling with mercury on alternate days, but carries out the irrigation with perhydrol solution less often, in order to avoid symptoms of irritation.

R. Roubitschek, Hall, H. Winternitz, Grodmann and Girardi report on the value of perhydrol in hyperchlorhydria. According to Roubitschek, the treatment is carried out like a course of mineral waters, beginning with a 0.5 p.c. solution of  $H_2O_2$ , 300 c.c. (10 oz) of which are taken on an empty stomach. If the acidity does not dis-

Walbum, Deutsche medizinische Wochenschrift 1911, p. 212 and Berliner klinische Wochenschrift 1911, p. 1929.

Marcuse, Berliner klinische Wochenschrift 1911, p. 1467.

Bickel, Berliner klinische Wochenschrift 1911, p. 1467.

Roubitschek, Deutsche medizinische Wochenschrift 1911, p. 374.

Hall, Boston Medical and Surgical Journal 1911, No. 24.

Winternitz, Deutsche medizinische Wochenschrift 1911, p. 1390.

Grodmann-Poly, Klinisch-therapeutische Wochenschrift 1911, p. 360.

Girardi, Gazzetta degli ospedali e delle cliniche 1910, No. 145.

appear after 3 doses, the strength of the solution is increased to 0.75 or 1 p.c. Eighty per cent. of the author's cases ended in a cure; in 20 p.c. of the cases, which were complicated by hypersecretion and disturbed motility, a cure did not result, so that the administration of  $\text{H}_2\text{O}_2$  evidently does not suffice in these cases. Usually a cure or a considerable improvement of the hyperchlorhydria may be reckoned on in the course of a fortnight, but the treatment may be continued for a longer time without harm. The author noticed a useful by-effect of perhydrol to be its mild purgative action; any constipation present in his cases usually disappeared. In 40 p.c. of the successfully treated cases, regulation of diet was required in addition to the course of perhydrol. As regards the duration of the successful result, the patients of Roubitschek, Hall and Poly\*) remained free from trouble during observations extending over many hours. Troublesome by-effects were not observed even on the prolonged use of  $\text{H}_2\text{O}_2$ , whereas Winternitz observed all kinds of gastric troubles after the administration to sensitive patients of a 0.5 p.c. solution on an empty stomach. For stomach lavage, especially in hypersecretion of acid accompanied by disturbed motility, he uses a 0.5 p.c. solution, more especially in the presence of acid fermentation. In this condition he also obtained good results by the use of magnesium-perhydrol. Girardi and Grodman also passed a favourable criticism on  $\text{H}_2\text{O}_2$  medication for hyperchlorhydria.

A new important indication for hydrogen peroxide medication is, according to G. Liebermeister, carcinoma of the œsophagus causing stenosis. He advises the following method of treatment: A 1 to 2 p.c. solution of  $\text{H}_2\text{O}_2$  is placed beside the patient's bed with the injunction to drink a mouthful of it every hour. Care is taken only to give the patients by mouth such food as will pass through the stenosed part. This treatment is continued for weeks and months. In absolute stenosis the patients are fed rectally and are given nothing but  $\text{H}_2\text{O}_2$  by mouth for 2 to 3 days. At the end of this time it is usually possible to begin the careful administration of liquid food by mouth. If this fails, morphine 0.01 gramme ( $\frac{1}{80}$  grain), or atropine 0.001 gramme ( $\frac{1}{64}$  grain), or the two combined, are given subcutaneously 3 times a day before meals for several days, e.g., 0.005 gramme ( $\frac{1}{12}$  grain) of morphine

\*) Compare Merck's Reprt 1910, p. 245.

Liebermeister, Münchener medizinische Wochenschrift 1911, p. 2016.

and 0.0005 gramme ( $\frac{1}{125}$  grain) of atropine for a dose. Treatment by sounds is only resorted to when all else fails. — By means of this treatment it is possible to keep the carcinoma free from products of decomposition and to change many an absolute stenosis into a relative one, indirectly to remove irritative conditions of the musculature of the œsophagus and to prevent secondary infections, sanious ulceration and possibly early perforations.

A summary of the many-sided employment of perhydrol in therapeutics has been published by Stock, and in it he recounts his own good results in the treatment of gonorrhœal infections in women. He gave daily injections of a 3 p.c. perhydrol solution through an opalescent glass speculum and allowed the liquid to remain for 5 to 10 minutes. When the discharge had quite disappeared, he continued for a time the introduction of tampons, which were soaked in perhydrol solution and changed twice a day. A communication by Grandoni is of interest and worth investigating; he obtained surprising results by means of irrigations with  $\text{H}_2\text{O}_2$  in puerperal infections. The author's treatment consists in a daily injection of 30 grammes (1 oz) of a 3 p.c.  $\text{H}_2\text{O}_2$  solution into the uterus. In a severe case he gave 6 injections, after which the general condition was remarkably improved and the obstinate fever disappeared. In other cases the author also obtained excellent results by means of this treatment.

The value of perhydrol in veterinary practice is clearly shown in the communications of Hummerich, Sustmann and Bouchet. Hummerich reports 2 cases of severe and obstinate wounds which were rapidly healed by syringing with a 5 or 10 p.c. perhydrol solution. In a short time the wounds became clean, the unhealthy areas disappeared and the dead tissue fibres were thrown off. Sustmann also obtained most excellent results in the treatment of wounds with perhydrol. The results obtained by Bouchet (and Bonnefous) by intravenous injection of  $\text{H}_2\text{O}_2$  in infective pneumonia of horses encourage further investigation. They injected pure, acid-

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Stock, Medico, 1911, No. 20.

Grandoni, Semaine médicale 1911, p. 467.

Hummerich, Zeitschrift für Veterinärkunde 1911, No. 6.

Sustmann, Berliner tierärztliche Wochenschrift 1911, p. 610.

Bouchet, Revue générale de médecine vétérinaire 1910, 1<sup>st</sup> July.

— Berliner tierärztliche Wochenschrift 1911, p. 525.

free, 12 volume  $\text{H}_2\text{O}_2$  (= 12 grammes [200 min.] of perhydrol + 88 grammes (3 oz) of water) into the jugular vein in doses of 10 to 180 c.c. ( $\frac{1}{3}$ —6 oz) once a day. This was followed by a severe reaction, consisting in restlessness, mild colic and attacks of suffocation, which lasted for a short period, after which the febrile temperature was reduced by as much as  $1^\circ\text{C}$ . and even severely ill horses could be rapidly cured.

Further communications on the employment of perhydrol for purposes of clinical and analytical investigation have been made by H. Salomon and P. Saxl, W. Migault, M. Dickert, A. von Maslow, A. Bochaix and L. Thévenon.

A reaction which is of some significance in the diagnosis of carcinoma is described by Salomon and Saxl. It consists in freeing the urine of the patient from sulphuric acid and ethyl sulphates by means of barium hydroxide and barium chloride, and converting the sulphur, which is usually present in the urine of cancer patients in the form of oxy-proteinic acids, into sulphuric acid by oxidation with perhydrol. This sulphuric acid will then, in course of time, with the excess of barium chloride present form a greater or less amount of precipitate of barium sulphate. The appearance of this precipitate signifies a positive reaction, and was obtained by the above named authors in 71 out of 81 cases. The value of this reaction in the diagnosis of cancer must naturally be confirmed by further investigations.

In elementary analysis, Migault recommends the employment of concentrated sulphuric acid and perhydrol for the oxidation of substances which are oxidised with difficulty, as for example the paraffins. In order to destroy organic substances, these are broken up and mixed with sulphuric acid in a suitable apparatus, into which the perhydrol is allowed to flow from a drop-funnel. The process of disintegration is aided by heating to  $100$  or  $140^\circ\text{C}$ . For 1 gramme of the substance, it is said that 2 to 4 c.c. of perhydrol and 6 to 12 c.c. of sulphuric acid are required.

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Salomon-Saxl, Wiener klinische Wochenschrift 1911, p. 449.

Migault, Chemiker-Zeitung, Vol. 34, p. 337.

Dickert, Journal für Gasbeleuchtung 1911, Vol. 54, p. 182.

Maslow, Zeitschrift für physiologische Chemie 1911, Vol. 74, p. 297.

Bochaix-Thévenon, Journal de pharmacie 1909, II, p. 573.

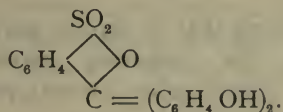
Dickert uses perhydrol for the estimation of the total sulphur in coal gas. The method depends upon the oxidation of sulphur into sulphuric acid on conducting coal gas through a mixture of 10 c.c. of perhydrol and 75 c.c. of caustic soda solution ( $30^{\circ}$  Bé = 25 p. c. NaOH). The sulphuric acid thus formed is either weighed as barium sulphate or estimated by titration. The advantages of this method are that it takes less time than other methods and that no flame is required, so that it can be carried out without danger in any department of a gas-works.

In place of Nakayama's reagent\*) for the demonstration of bile pigments in the urine, Maslow makes use of a modified reagent, in which iron chloride is replaced by perhydrol. The urine to be tested is added to barium chloride solution and poured off the precipitate which is formed. Then alcohol containing 1 p.c. of nitric acid and a few drops of dilute perhydrol are added to the precipitate and the mixture is heated to boiling. In the presence of bile pigment the mixture assumes a dark bluish-green colour.

According to Bochaix and Thévenon, boiled and unboiled milk can be distinguished by a simple method. For this purpose the albuminates are precipitated by the addition of acetic acid and magnesium sulphate, and the mixture is filtered. To 2 c.c. of the filtrate 4 to 5 drops of a perhydrol solution (12 + 88) and 2 to 3 c.c. of a 4 p.c. pyramidon solution are added and the mixture is carefully warmed. With this test unboiled milk gives a transient violet coloration.

### Phenolsulphonephthalein.

Phenolsulphonephthalein, described by Remsen and later by Sohön, forms a light red, crystalline powder, soluble with difficulty in water, more readily soluble in alcohol and alkalies. It crystallises from acetic acid in the form of needles, which appear bluish-green by reflected light and deep red by transmitted light. It has the chemical formula



\*) Compare Merck's Reagenzien-Verzeichnis 1908, p. 183.

Remsen, American Chemical Journal 1884/85, Vol. 6, p. 180.

Sohön, American Chemical Journal 1889, Vol. 20, p. 263.

J. T. Geraghty and L. G. Rowntree have found that phenolsulphonephthalein is a useful reagent for testing the functions of the kidneys. As, according to Abel and Rowntree, it is non-poisonous, it may be employed subcutaneously, intramuscularly or intravenously. It is excreted by normal kidneys a few minutes after being taken, while in nephritic affections the excretion is more or less delayed. The commencement of its elimination in the urine can readily be recognised in that the urine, on being rendered alkaline by caustic soda, assumes a reddish to deep red coloration.

The examination of the kidneys themselves is carried out as follows: About 20 to 30 minutes before the employment of phenolsulphonephthalein, the patient is given 300 to 400 c. c. of water. Then, with aseptic precautions, the bladder is emptied by means of a catheter. Now a solution of 0.006 gramme of phenolsulphonephthalein in 1 c. c. of water is injected subcutaneously or intravenously. The time is then calculated which elapses between the injection and the assumption by the urine of a reddish coloration on the addition of caustic soda. The patient is instructed to pass urine into separate vessels at regular intervals, in order that the urine passed at fixed intervals may be tested for phenolsulphonephthalein by suitable colorimetric means. For this purpose a fluid is prepared for comparison which contains 6 grammes of phenolsulphonephthalein in a litre. It is best to add caustic soda to the urine and standard solution before carrying out the colorimetric estimation, as the red colour of the alkaline phenolsulphonephthalein solution may lose in intensity on long standing under the influence of caustic soda.

After the subcutaneous injection of the drug in persons with normal kidneys 38 to 60 p. c. of the injected phenolsulphonephthalein appear in the course of the first hour, and 60 to 85 p. c. in the course of two hours. After this time, in healthy individuals, only traces of the reagent are usually found.

The authors found that in chronic parenchymatous nephritis the excretion of the colouring matter was delayed, in severe cases to a considerable extent; indeed, in very severe

cases, they were only able to demonstrate traces of the reagent; thus, in severely diseased kidneys it is almost completely retained. In interstitial nephritis and uræmia retardation of the excretion was also observed, while the authors' experiments in acute nephritis do not suffice to form a reliable opinion.

The authors consider that their method of investigation possesses many advantages over other similar methods, and these they attribute to the good qualities of phenolsulphone-phthalein, e. g., the ease with which even traces can be demonstrated, simple quantitative estimation and rapid elimination from the organism without toxic action. Its chief value is that functional disturbances of the kidneys can be shown to exist, not only in cases which have been already diagnosed, but also in diseases of the heart and kidneys not yet recognised; and that it is possible to say whether both kidneys are functionally disturbed or only one, and if so, which one, which is a matter of great importance for contemplated operations.

### Phlorhizin.

The altered method of spelling this preparation in my list has given rise to enquiries, as it was supposed that phlorhizin and phloridzin were different preparations. We cannot here discuss how the incorrect method of spelling "phloridzin" came to be adopted, but neither is there any reason why this method should be retained. The word is derived from the two Greek words "*φλοιός* = bark of a tree", and "*ρίζα* = root". From this it follows that the only correct method of spelling is "phlorhizin".

As phlorhizin has not before been mentioned in my Reports and as it is of increasing interest, the most important data in the literature will be given.

Phlorhizin is a glucoside obtained from the bark of apple, cherry and plum trees, having the chemical formula  $C_{21}H_{24}O_{10} + 2H_2O$ . It forms white needles, soluble in alcohol and hot water, which melt at  $108^{\circ}C.$ , solidify again at  $130^{\circ}C.$ , and melt once more at  $170^{\circ}C.$  On hydrolysis, phlorhizin yields glucose and phloretin. Phloretin forms an almost white powder, soluble in alcohol and alkalies, which melts at  $253^{\circ}C.$  with decomposition. On boiling with alkalies it is gradually

changed into phloretinic acid and phloroglucin. (Merck's Report 1888, p. 44.) A more detailed account of the chemistry of phlorhizin may be found in the publications of de Koninck, Petersen, Cremer and Schiff. M. Cremer has recently succeeded in breaking up phlorhizin into phloretinic acid and phloroglucin-glucoside. The latter he named phlorin. It is a crystalline body, similar in physiological action to phlorhizin.

Phlorhizin became of interest in physiology after von Mering had discovered that the suitable administration of this preparation to dogs gave rise to artificial diabetes, so-called phlorhizin-diabetes. According to the author's experiments, it is possible, by several days' starvation and the simultaneous administration of 1 gramme of phlorhizin pro kilogramme of body-weight, to render the animals so free from glycogen that no glycogen can be demonstrated either in the muscles or in the liver, and on continuing the experiment, a considerable amount of glucose appears in the urine of the animals. In the absence of the administration of carbohydrates this sugar, according to von Mering, can only be derived from disintegrated albumin or from meat. It has also been shown that diabetes can be brought about in human beings by doses of only 0.2 gramme of phlorhizin, without causing any marked disturbance of health. The amount of sugar in the blood, according to von Mering, is diminished in phlorhizin-diabetes, which points to its being due to a transient change in the kidneys, which influences the excretion of glucose.

A large number of observers have followed von Mering in investigating phlorhizin-diabetes and its origin from the action of phlorhizin, but they do not all entirely agree with Mering's conclusions. As it would lead too far to consider in greater detail here a subject which can but interest the specialist, reference will be made to the more important bibliography on the subject:

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de Koninck, Liebigs Annalen 1835, Vol. 15, p. 75.

Petersen, Liebigs Annalen 1835, Vol. 15, p. 178.

Cremer, Zeitschrift für Biologie, Vol. 36, p. 115.

Schiff, Zeitschrift für Chemie 1870, Vol. 5, p. 708. — Chemisches Zentralblatt 1871, p. 297.

Cremer, Münchener medizinische Wochenschrift 1911, No. 32, p. 1713.

- Mering, Verhandlungen des 5. and 6. Kongresses für innere Medizin 1886 and 1887. — Lehrbuch der inneren Medizin 1907, p. 1065.  
— Zeitschrift für klinische Medizin 1888, p. 405 and 1889, p. 431.  
Mering-Minkowski, Archiv für experimentelle Pathologie 1889, Vol. 26, p. 371. — Berliner klinische Wochenschrift 1890, No. 8.  
Minkowski-Thiel, Archiv für experimentelle Pathologie 1887, Vol. 23, p. 142.  
Moritz-Prausnitz, Zeitschrift für Biologie, Vol. 27, p. 81 and Vol. 29, p. 168.  
Cremer-Ritter, Zeitschrift für Biologie, Vol. 28, p. 458, Vol. 29, p. 275, Vol. 37, p. 59.  
Pick, Archiv für experimentelle Pathologie 1894, Vol. 33, p. 313.  
Zuntz, du Bois-Reymonds Archiv 1895, p. 570.  
Hellin-Spiro, Archiv für experimentelle Pathologie 1897, Vol. 38, p. 368.  
Geelmuyden, Zeitschrift für physiologische Chemie, Vol. 26, p. 381.  
Schwarz, Archiv für experimentelle Pathologie 1900, Vol. 43, p. 26.  
Kossa, Zeitschrift für Biologie Vol. 40, p. 324.  
Loewi, Archiv für experimentelle Pathologie 1902, Vol. 47, p. 48.  
Külz-Wright, Zeitschrift für Biologie, Vol. 27, p. 81.  
Knopf, Archiv für experimentelle Pathologie 1903, Vol. 49, p. 123.  
Henderson-Loewi, Archiv für experimentelle Pathologie 1905, Vol. 53, p. 49.  
Loewi, Archiv für experimentelle Pathologie 1903, Vol. 50, p. 326.  
Zegla, Biochemische Zeitschrift, Vol. 16, p. 111.  
Glaessner-Pick, Hofmeisters Beiträge zur chemischen Physiologie und Pathologie 1907, Vol. 10, p. 473.  
Lewandowsky, du Bois-Reymonds Archiv für Anatomie und Physiologie 1901, p. 365.  
Yokota Hofmeisters Beiträge 1904, Vol. 5, p. 313.  
Pavy-Brodie, Journal of Physiology 1903, Vol. 29, p. 467.  
Leschke, (Verhalten des Phlorhizins nach der Nierenexstirpation) Pflügers Archiv für die gesamte Physiologie 1910, Vol. 132, p. 319.  
Schöndorff-Suckrow, Archiv für die gesamte Physiologie, Vol. 138, p. 1.  
Grube, Archiv für die gesamte Physiologie, Vol. 139, p. 165.

None of these publications give special indications for the therapeutic employment of phlorhizin, though the diuretic action of the drug cannot be denied. It may be noted that Loewi does not consider the drug to be a direct diuretic. Diuresis, according to his experiments, is due to an indirect action of phlorhizin in the following manner: "The sugar liberated in the epithelium by means of phlorhizin and separated out into the lumen of the tubules, by reason of its hygroscopic properties and the difficulty of its resorption, retains the water in the tubules, which is filtered in normal amount through the glomeruli, and prevents its re-absorption."

The only suggestion which has come to my notice of employing phlorhizin therapeutically was made by Koniak, who used it in doses of 0.6 to 1 gramme (10—15 grains) internally as an antipyretic (malaria) in place of quinine (Compare Merck's Index 1908, p. 215 and Hager's Handbuch der Pharmazeutischen Praxis 1902, II, p. 591).

Of far greater significance is the employment of phlorhizin as a functional test for the kidneys, depending on the property possessed by the preparation of exciting diabetes. Casper and Richter found that the appearance of sugar after an injection of phlorhizin before or after operations on the kidney was of considerable diagnostic value. Their method consists in catheterising both ureters, giving a subcutaneous injection of phlorhizin and then testing the urine from both ureters quantitatively for glucose. If sugar be absent from the urine, it is a sign of considerable functional disturbance of the kidney. The greater the amount of sugar found, the more functioning kidney parenchyma is present. The authors state that the total amount of sugar excreted, the time which elapses between the injection of phlorhizin and the beginning of glycosuria, its duration and comparisons between the absolute amount and the amount per cent. of glucose in the urine in equal periods of time constitute important points in judging the renal function. But these possibilities were partially discredited by various other observers, including Albarran, Israel, Kapsammer and Zuelzer, who were able to demonstrate that the two ureters can excrete different amounts of sugar in the same time, so that even under normal conditions the comparison between the absolute amount and the amount per cent. of sugar, designated by Casper as of special importance, is fallacious. The proof furnished by the duration and the commencement of sugar excretion after the injection of phlorhizin was also doubted by some authors. Kapsammer, therefore, modified the phlorhizin test by determining with greater exactitude the time of appearance of glycosuria after the injection. He states that a kidney is

Casper-Richter, Funktionelle Nierendiagnostik 1901. — Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie 1903. Albarran, Thèse de Paris 1905.

Kapsammer, Nierendiagnostik und Nierenchirurgie. Vienna 1907. Archiv für klinische Chirurgie, Vol. 79, No. 3. — Wiener klinische Wochenschrift 1906, p. 1415, 1908, p. 815 and 1377.

functioning normally if sugar can be demonstrated at the longest 15 minutes after the injection. The hypothesis advanced by him in explanation of the test is as follows: The phlorhizin method, the time of appearance of sugar being noted, represents the most delicate and simple reaction which we at present possess for testing the function of the kidney. The many histological investigations which have been carried out have shown the proportional relationship between the time of appearance of sugar and the severity of the anatomical lesion. The greater the pathological changes, the longer is the appearance of sugar delayed. If the sugar appears 12 to 15 minutes after the injection of 0.01 gramme ( $\frac{1}{6}$  grain) of phlorhizin, it signifies a kidney which is healthy or capable of functioning, provided there be no parenchymatous nephritis as shown by the presence of albuminuria and casts. If the total urine shows sugar 10 to 15 minutes after the injection, it signifies that at least one kidney is capable of functioning. If no sugar be found in the total urine until 30 minutes after the injection, considerable functional disturbance of both kidneys is present; and if 45 minutes after the injection no sugar be found, this signifies functional disturbance of both kidneys which is of such severity that successful nephrectomy seems out of the question."

Von Haberer, Lichtenstern, Rovsing, Blum and Prigl and Lenk do not agree with Kapsammer's method. In spite of which Kapsammer upholds it, though he agrees with von Haberer in asserting that the phlorhizin method, like all other functional tests, does not indicate the actual seat of disease, but only indicates damage of the parenchyma in general; it only allows the seat of disease to be recognised if this has caused damage to the renal parenchyma. Even though the method makes no great claims, yet it is, in his opinion, the best at present known.

As phlorhizin is only soluble with great difficulty in cold water (about 1:500), it is best to use a 1 p.c. solution in warm water or in normal saline solution, which is prepared

Haberer, Wiener klinische Wochenschrift 1906, p. 823.

Lichtenstern, Wiener klinische Wochenschrift 1906, p. 1484; 1908, p. 843.

Rovsing, Archiv für klinische Chirurgie 1905.

Blum-Prigl, Wiener klinische Wochenschrift 1908, p. 1445.

Lenk, Wiener klinische Wochenschrift 1908, p. 756.

immediately before use and is allowed to cool to body temperature before injection. The dose of this is 1 c.c. If it be desired to keep a 1 p.c. solution in stock, it must always be boiled before use, so that the phlorhizin which has separated in the cold is redissolved.

It is possible that the phlorhizin method may be found of diagnostic significance in cases of Graves's disease and thyroidism which are difficult of recognition. This at least may be concluded from the communications of Caro.

### **Picric Acid.**

In A. Ehrenfried's experience, picric acid has proved an excellent antiseptic in surgical practice. In 1-2 p.c. aqueous solution it kills virulent cultures of bacillus pyocyaneus and of staphylococcus pyogenes aureus in half to two minutes, and is therefore 50 times more powerful than a 1 p.c. solution of carbolic acid. Picric acid has been found useful not only in burns, for which it has been employed for many years, but also for wounds of various descriptions and for granulating sores. The best method of application is in the form of a saturated aqueous solution of the chemically pure acid (about 1-2 p.c.); it is applied on cotton wool soaked in the solution. In burns of the first and second degree the hands or feet may be dipped in this solution for several minutes and then bound up in cotton wool and a waterproof bandage. But this treatment is only suitable for superficial wounds and for burns of the first and second degree, and not for burns of the third degree in which large areas of skin are affected. If before applying the picric acid dressing the wounds are well cleansed and freed from pus, they will heal in a few days without any fear of toxic symptoms supervening.

Marzorati expresses himself very satisfied with the value of picric acid in burns and caustic injuries of the cornea, and thus confirms the observations of Fortunati and others.

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Caro, Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie 1911, Vol. 23, No. 1. — Medizinische Klinik 1911, p. 1287.

Ehrenfried, Journal of the American Medical Association 1911, p. 412 (11<sup>th</sup> February). — Nouveaux remèdes 1911, p. 341.

Marzorati, La Clinique 1910, No. 49. — Wochenschrift für Therapie und Hygiene des Auges 1911, Vol. 14, p. 103.

Fortunati, Merck's Report 1910, p. 71.

In treating 21 cases of corneal wounds resulting from burns caused by lime, sulphuric acid, hydrochloric acid, caustic alkali, hydrofluoric acid, liquid metal, gas explosions and hot air, the aqueous solution of picric acid was found of great service. Even in superficial corneal ulcerations affecting the entire cornea it brought about a cure in 3 to 4 days without leaving any opacity. But in severe cases it is not of great benefit. Its use is on the whole simple. After the eye has been washed and the corroding substance removed, the solution is instilled and a suitable bandage applied. Seeing that the acid acts as an antiseptic and sedative and promotes the formation of horny skin, the author considers himself justified in recommending its use in other corneal sores.

Schamberg and Kolmer tested the use of a 4 p. c. alcoholic solution of picric acid for inflammatory conditions of vaccination pustules. This prophylactic measure, employed 48 hours after vaccination, is said to yield good results without unfavourably influencing the result of the vaccination.

### Podophyllin.

Chologen\*), the active components of which are podophyllin and calomel, was last year reported upon by H. Kehr, Ludewig, P. Ilse, Fackenheim, Berg and van Elsbergen. Kehr puts chologen aside, asserting that it has only an aperient action and is of no use for the cure of gall-stones. In his opinion, the drug, provided it has any beneficial effect at all on bile, can only be of use if the cystic duct is pervious, in which case the patients are free from symptoms. These only appear when the neck of the gall-bladder is blocked. The author, on the ground of autopsies carried out by him in vivo, doubts whether chologen is of any use in these cases. He also absolutely denies that the drug has any action on the stones. Ludewig, on the other hand, asserts that in consequence of treatment with chologen the stones

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Schamberg-Kolmer, *Lancet* 1911, 18<sup>th</sup> November, p. 1397.

\*) Compare Merck's Report 1904.

Kehr, *Münchener medizinische Wochenschrift* 1911, p. 609.

Ludewig, *Allgemeine medizinische Zentral-Zeitung* 1911, p. 297.

Ilse, *Klinisch-therapeutische Wochenschrift* 1911, p. 801.

Fackenheim, *Deutsche Medizinalzeitung* 1911, p. 747.

Berg, *Deutsche medizinische Wochenschrift* 1911, p. 7375

Elsbergen, *Medizinische Klinik* 1911, p. 384.

lose their sharp edges and that their passage thus causes less pain. In his opinion, the patients can not only be freed from stones with the help of chologen, but it will also cure inflammatory adhesions. He makes the condition, however, that the treatment must not be carried out mechanically, but that individuality must be considered. If correctly used he states that the preparation only acts as a purgative during the first 3 days. The author attempted to prove experimentally that the bile, being improved by chologen, is capable of softening and rounding off the stones, by placing stones in the fresh bile of swine to which chologen had been added and observing its action at the body-temperature. This is said to have rendered the stones friable. (Criticism of the conclusiveness of an experiment of this nature and of the experiment itself, I must leave to more competent persons.) Ilse also seeks in chologen the active principle for dissolving the stones in treatment with chologen, while Kehr asserts that the stones are rendered soft, not by the chologen, but by the infection. Elsbergen, who has obtained very good results by chologen treatment systematically carried out for years, has come to the conclusion that chologen has most probably, on the one hand, a certain influence on the solution of the substance of the gall-stones, and on the other hand, exerts a qualitative action on the bile of such a nature that stones are either prevented from being formed or are not so readily formed. Fackenheim and Berg were also satisfied with the action of chologen.

### Pomegranate, Extract of

C. Glücksmann has worked out the following method for the identification of the extract of the bark of the root of pomegranate: A few milligrammes of the extract are dissolved in 5 to 10 c.c. of dilute glycerin warmed on a water-bath; the solution is diluted in a test-tube by adding distilled water until the yellow colour seen by transmitted light just disappears, and a test-tube is filled three-quarters full with this solution. The addition of 1 to 2 c.c. of lead acetate solution (1:10) causes a canary yellow coloration. The mixture remains yellow when viewed by transmitted light and is apparently clear, but if filtered a colourless filtrate is obtained, while a yellow precipitate remains on the filter paper. The

yellow coloration of the filter paper is said to be particularly noticeable on drying. As, according to the investigations of the author, no other official extract gives the reaction described, it may be considered specific for extract of pomegranate.

#### Potassium and Sodium Bromide.

The question as to whether in epilepsy sodium bromide or potassium bromide is preferable, presuming that an inorganic salt of bromine is to be chosen, has been discussed by P. Jödicke. He came to the conclusion that the potassium salt was to be preferred. He bases this upon the fact that potassium bromide affords the best means of freeing the system from chlorine and thus obtaining the desired therapeutic action; for the two components of the salt contribute to the rapid excretion of sodium chloride through the kidneys. Further, he does not consider it proven that the internal administration of potassium bromide may damage the circulatory apparatus. He also states that, in Germany at any rate, larger doses, such as 15 grammes ( $1\frac{1}{2}$  oz), which might cause cardiac disturbance, are never employed.

#### Potassium Chromate.

A 10 p.c. aqueous solution of potassium chromate is used by H. Weil as a test for the salts of nickel and cobalt. Cobalt solutions which contain more than 0.2 p.c. of cobalt give with the reagent a brownish-red precipitate of basic cobalt chromate at the ordinary temperature; with more dilute solutions this is only obtained on heating to boiling. The precipitate ( $\text{CoCrO}_4 \cdot \text{CrO}$ ) is only soluble in ammonia and acids, and not in caustic alkalies. The limit of sensitiveness of the reaction is represented by 0.000032 gramme of cobalt. The corresponding basic salt of nickel ( $\text{NiCrO}_4 \cdot 2\text{NiO}$ ), even in higher concentration, is formed very slowly at the ordinary temperature, and for its rapid formation requires to be heated to boiling. It only sticks very slightly to the test-tube, whereas the cobalt compound adheres fairly firmly to the glass. The limit of sensitiveness of the nickel reaction is 0.000028 gramme of nickel. The reaction is naturally only obtained in a neutral solution. If nickel be present in great preponderance as

Jödicke, *Medizinische Klinik* 1911, p. 569.

Weil, *Bulletin de la société chimique de France* 1911, Vol. 9, p. 20.

compared with cobalt (50 times as much), the basic cobalt chromate is held in solution and is not precipitated at the ordinary temperature; if cobalt be present in larger quantity, the presence of both metals can be demonstrated without difficulty.

### Potassium Hexatantalate.

Potassium hexatantalate,  $K_8Ta_6O_{19} + 16H_2O$ , a salt soluble in water, was investigated by J. Morgenroth and F. Rosenthal with regard to its trypanocidal action, as the relationship of tantalum to arsenic and antimony suggested the probability that it would display an action similar to that of the compounds of arsenic and antimony. The result of these investigations showed that this salt of tantalum is comparatively slightly toxic, and in experiments on animals showed no trypanocidal action. On the other hand, by intensive treatment of a trypanosome stock with potassium hexatantalate, it is possible to endow it with a certain power of resistance to antimony (antimonyl potassium tartrate). Morgenroth draws the conclusion that in spite of the absence of a trypanocidal action of the tantalum compound, it does act on the trypanosomes, inasmuch as their substratum, if Ehrlich's view be accepted, viz., the chemoceptors of the trypanosomes are the same as those which form the receptors for the antimony compounds. The fact that tantalum exerts a direct influence on the trypanosomes and their vital functions is apparent, according to the authors, in that prolonged treatment with tantalum, although it does not interfere with their multiplication in the circulation, yet is capable of injuring their inoculability. Another important discovery of Morgenroth's is that the trypanocidal action of antimonyl potassium tartrate is counteracted in the body of the mouse by potassium hexatantalate. Besides, the general toxic effect of tartar emetic on the mouse is interfered with by the tantalum salt. The conditions under which this reaction takes place as regards amounts and time, as well as the reciprocal behaviour of both compounds in solution, make a direct mutual influence seem probable, so that potassium hexatantalate, or possibly one of its derivatives produced in the animal body, appears to be the true antidote to the antimony compound, acting in the circulation.

Morgenroth-Rosenthal, *Zeitschrift für Hygiene und Infektionskrankheiten* 1911, p. 506.

### Potassium Iodate.

For the qualitative determination and for the quantitative estimation of thorium, R. J. Meyer makes use of two solutions of iodic acid in nitric acid, which precipitate thorium salts in the form of thorium iodate. For this purpose the following two solutions are prepared: a solution of 15 grammes of potassium iodate in 100 c.c. of water and 50 c.c. of nitric acid (sp. gr. 1.4), and a solution of 4 grammes of potassium iodate in 400 c.c. of water and 100 c.c. of nitric acid (sp. gr. 1.2). The thorium solution to be tested must be free from hydrochloric acid. 2 c.c. of it are mixed with 5 c.c. of the concentrated iodic acid solution, whereby a precipitate of thorium iodate is formed. If salts of cerium and yttrium be present, they may also be partially precipitated in the form of iodates. For this reason the mixture is diluted with 10 c.c. of the dilute iodic acid solution and heated to boiling. To obtain a satisfactory reaction a large excess of the precipitant should be present, so that the solubility of the thorium iodate is reduced to a minimum and that sufficient nitric acid is present to keep in solution the iodates of the earths already named. This is the explanation of the employment of concentrated and dilute solutions of iodic acid. By the method described the thorium iodate remains undissolved, even if more of the dilute iodic acid solution be subsequently added. The limit of sensitiveness is represented by 0.1 gramme of thorium oxide in a litre of solution. As cerium salts are likewise precipitated by iodic acid, these must be reduced before the test is applied, and the simplest method is to boil with sulphurous acid. If zirconium iodate be present it can be dissolved by oxalic acid.

### Potassium Nitrate.

R. G. Ferrer and J. T. Pedragosa report upon the excellent results obtained by them by the administration of potassium nitrate in measles. The drug gives most promise of success when given early, as, in Ferrer's opinion, it possesses antitoxic properties, in consequence of which it reduces

Meyer, *Zeitschrift für anorganische Chemie* 1911, Vol. 71, p. 65.

Ferrer, *Revista de especialidades medicas* 1911, 1<sup>st</sup> February. —

*Cronica medica* 1910, 25<sup>th</sup> November. — *Revue internationale de médecine* 1911, p. 277.

Pedragosa, *Siglo medico* 1911, 7<sup>th</sup> January.

the temperature, heals the rash and prevents the occurrence of complications in the lungs, the bowels and the brain. It may also be used with advantage as a prophylactic against measles and as a preventive against recurrences. It is apparently of no use in mixed infections. The drug should only be used for children over 3 years of age. The dose for children of 3 to 4 years is 0.25 to 0.35 gramme ( $4-5\frac{1}{2}$  grains) a day, 4 to 5 years, 0.35—0.5 gramme ( $5\frac{1}{2}-7\frac{1}{2}$  grains), 5 to 8 years, 1—1.5 grammes (15—24 grains), 8 to 12 years, 1.5 to 2 grammes (24—30 grains), and of 12 to 15 years, 2 to 3 grammes (30—45 grains). Ferrer gave up to 1 gramme (15 grains) 3 to 4 times a day to adults and never observed troublesome secondary effects.

### Potassium Tellurate.

Potassium tellurate,  $K_2TeO_4 + 3H_2O$ , has according to Ochmann, proved useful against the molestation of horses, donkeys and dogs by flies. After the internal administration of the preparation the expired air, the skin and the fæces are said to assume an objectionable, garlic-like smell (methyl telluride), which keeps the flies away. The animals take the preparation in their food without trouble, and it does not display any troublesome by-effects. Although it must be admitted that a really good means of driving away flies, especially in stables, would be a valuable addition to other hygienic measures, yet the high price of potassium tellurate would stand in the way of its general adoption. Besides, A. Mayer has experimentally proved that horses and cows, after having taken 1 to 5 grammes (15—75 grains) of potassium tellurate and a total dose of 10 grammes ( $\frac{1}{3}$  oz), are molested by flies just as much as before. The garlic-like smell of the expired air was only present in one cow and lasted for some time in this case; in the horses the drug either did not act at all or only very feebly and for a brief period.

On the other hand, according to Mayer, inunction with fresh, non-rancid laurel oil has proved useful; according to the extent of the cutaneous surface to be treated, it is applied either alone or mixed with 9 parts of olive oil, or with 5 parts of olive oil and 4 parts of dilute spirit,

and is lightly rubbed in. The author's experience shows that the drug is not unduly irritating and does not cause the hairs to fall out, for he caused it to be rubbed hard into the coronet of horses and an area of skin 2 cm. broad over it for 10 minutes on alternate days for six months and more without the hairs falling out. The results obtained by Mayer with decoctum quassiae and the so-called floria fly oils were not very encouraging.

### Primal.

That a demand exists for a really useful hair-dye is evident from the fact that the use of paraphenylenediamine, which was found shortly after its introduction as a hair-dye to irritate the skin, was only suppressed with difficulty. It is well known that legal measures had to be adopted for this purpose. In order to render paraphenylenediamine and related bases non-poisonous, Tomaszewski and Erdmann introduced a sulphone group into the molecule of these bases, which made it possible to use these substances, such as o-amino-phenol-sulphonic acid and p-amino-diphenylamine-sulphonic acid, as harmless hair-dyes which are hygienically free from objection. Later, Wolfenstein and Colman succeeded in rendering the toxic amines harmless by a more simple method, viz., by changing the base (Brandowski's base) formed by oxidation of paraphenylenediamine into the corresponding leuco-base by reduction and applying this to the hair which required dyeing. The desired effect was obtained, and as by this procedure the skin does not come into contact with the toxic amines, no cutaneous irritation results. This method was simplified by the investigations of Colman and Loewy, who found that the amines could be detoxicated by the addition of certain reducing substances, without losing their properties as dyes. Rather do the detoxicated amine bases form a real hair-dye after oxidation, dyeing from blond to black according to the amount of base and oxidising agent (hydrogen peroxide) chosen. The best combination for a hair-dye has proved to be a solution of p-toluylene-diamine with neutral sulphites, which is put on the market under the name of "primal".

Tomaszewski-Erdmann, Münchener medizinische Wochenschrift 1906, p. 359. — Merck's Report 1906, p. 99.

Colman-Loewy, Deutsche medizinische Wochenschrift 1911, p. 926.

The experiments which have been carried out by Loewy on human beings and animals show with certainty that primal is a harmless preparation.

### Protargol.

E. Freund reports upon the employment of protargol in gonorrhœa of women. If cystitis were present at the same time, he emptied the bladder and introduced into it by means of a catheter 50 grammes ( $1\frac{2}{3}$  oz) of a 0.25 p.c. solution and also irrigated the urethra with this solution on withdrawing the instrument. By immediately emptying the bladder the urethra was once more brought into contact with the silver solution. If cystitis were absent, he treated the urethritis by prescribing irrigations of the urethra with a protargol solution 3 times a day, the strength of the solution being gradually increased. By this method he obtained very satisfactory results and even in the presence of the complication mentioned, the gonorrhœal process was cured in 2—3 weeks.

For the treatment of male gonorrhœa, E. Kuhn recommends removing the pus within the first few days, in order to prevent an upward extension of the infection. In his opinion, more depends upon this than upon the destruction of the gonococci by strong antiseptics. The pus may be removed by commencing the treatment with frequently repeated irrigations with protargol solution, which is diluted sufficiently to prevent irritation. The author applied the solution every half hour during the day, and in severe cases even every quarter of an hour, and at least every hour during the night. Before injecting the protargol solution, the patient should always first pass urine, and in order to effect this he should take as much fluid as possible. By means of this treatment the pus disappears in the course of 3 to 5 days. But in spite of this, the irrigations should be continued for at least 2 to 3 weeks, although their frequency may be diminished during the night.

For commencing gonorrhœa, in which inflammatory symptoms have not yet developed, Carle prescribes 3 injections

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Freund, *Klinisch-therapeutische Wochenschrift* 1910, No. 48.

Kuhn, *Münchener medizinische Wochenschrift* 1911, No. 37.

Carle, *Revue des maladies des organes génito-urinaires* 1911, Vol. 7, No. 42.

a day of a 1 to 2 p.c. protargol solution. In severe inflammation with discharge, he gives injections of a 1 p.c. ichthyol solution for the first few days and then 2 ichthyol and 2 protargol injections a day. Should symptoms of irritation appear, ichthyol injections may be substituted for protargol. After 10 to 15 days of treatment, the injections are gradually reduced, but they should not be stopped suddenly, even in the presence of an apparent cure.

### Pyoktanin.

Pyoktanin was used by A. Leber and S. von Prowazek for the treatment of an infective disease of the conjunctiva occurring in the Samoan Islands for which the authors suggest the designation epitheliosis desquamativa. Recent infections could generally be favourably influenced by instillations of a pyoktanin solution 1:100 or 1:1000.

In an instructive paper, Stilling explained the great value of pyoktanin as an antiseptic in general, and in foot-and-mouth disease of cattle in particular. From this it may be seen that the preparation is not only of excellent service in veterinary practice, but is worthy of more notice in human medicine, as it possesses the advantage over other known antiseptics, as for example corrosive sublimate, of displaying a healing as well as a prophylactic action; it destroys pathogenic bacteria, without at the same time precipitating albumin. The intense staining power of pyoktanin is alone responsible for its not having long ago replaced the antiseptics in common use in therapeutics. In veterinary medicine, in which this purely external disadvantage of the preparation is of less importance, its value has long been fully recognised. Here it is greatly prized in the treatment of suppurating wounds, pressure sores and other affections. Suppurating wounds, so long as they are perfectly accessible, are, according to Stilling, healed in a remarkably short time by treatment with pyoktanin.

Pyoktanin was recommended by Stilling as long as 20 years ago for the treatment of foot-and-mouth disease and has since been employed with the best results. In my Annual

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Leber u. Prowazek, Berliner klinische Wochenschrift 1911, No. 5.  
Stilling, Landwirtschaftliche Zeitschrift für Elsaß-Lothringen 1911,  
No 26.

Report for 1890 I quoted the exact method of use as described by Mehrdorf. It is founded upon the original statements of Stilling, who at first used pyoktanin in 0.1 p.c. solution. Now Stilling states that far higher concentrations may be used, up to 5 p.c. and stronger. Even the pure substance may be sprinkled on to parts which are easy of access. This applies especially to diseases of the external cutaneous surfaces. For diseases of the mucous membranes, on the other hand, solutions should be used, as the pure substance may cause irritation and hyperæmia of these parts. Therefore, in diseases of the mouth, Mehrdorf's instructions should be followed, whereas in diseases of the feet and the udder strong (5 to 10 p.c.) solutions, and in open accessible wounds the pure substance should be chosen. The pyoktanin method of treatment should be further developed in severe cases by laying bare the affected parts and thus making them more accessible to the action of the drug. S. Galbusera also considers intimate contact of pyoktanin with the diseased part to be necessary in order that satisfactory results may be obtained. To attain this end, the tongue, palate, lips, etc., should be freed from epithelial scales and all diseased parts washed several times with fresh water before applying the drug. This author also is in favour of the use of stronger solutions than were formerly recommended. His results were most satisfactory, and the action was promptly displayed. Animals which for several days had taken no nourishment, began to eat immediately after the treatment. The same success was also recorded in animals in which the interior of the mouth, the lips and the nostrils constituted a single extensive wound surface. By the daily employment of pyoktanin the formation of a new epithelial layer was hastened, so that a return to the normal was rapidly obtained. Care must, of course, be taken that the food given at first is easy to chew, so that the wound surfaces may not be too greatly irritated. More attention should also be paid to the prophylactic employment of pyoktanin. J. Heinrich Klein has already successfully carried this idea into practice. He started from the assumption that the mouth and teeth are the parts most liable to infection, and the therefore attempted to render the infective material

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Galbusera, *La Clinica Veterinaria* 1911, No. 23.

Klein, *Berliner tierärztliche Wochenschrift* 1911, p. 645.

innocuous to these parts by treating them with a 2 p.c. alcoholic solution of pyoktanin (cœruleum). This procedure is aided by the property possessed by the drug of strongly staining the parts with which it comes into contact, for on the disappearance of the intense coloration the time for renewed application has arrived. On the appearance of the epidemic, the author had his whole stock of cattle, even the youngest calves, treated with pyoktanin solution; after a thorough cleansing of the clefts and crests of the hoofs these were well painted with the solution. In the same way the mucous membranes of the nose and the lips were painted, and a brush, well soaked in the solution, was introduced several times into the mouth so that the animals, by constant licking, distributed the colouring matter to all parts with their tongues, and the mucous membranes and especially the tongue were thus coloured blue. This treatment protected all the animals from acquiring the disease, which had broken out in the district and prevailed there for three months. Even if this experiment furnishes no absolute proof of the antiseptic power of the treatment described, yet the author's assumption is well founded that by the prophylactic employment of pyoktanin the danger of infection is considerably diminished. Further tests of his method may be recommended.

Mention may be made of a communication by Dun, who used pyoktanin as an antiseptic dressing after the resection of the flexor tendon of the hoof of a cow. By this treatment the bone defect granulated within 14 days, and 3 weeks later the animal could again be used for draught purposes.

### Quinine.

Useful hints for the drug treatment of malaria, and especially for the administration of quinine, have been published by H. Werner. He states that it is a matter of prime importance to give the quinine in a form in which it is readily absorbed; thus, if it be given in capsules, only those should be used which are easily opened in the digestive tract. It is of minor importance whether the preparation

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Dun, Münchener tierärztliche Wochenschrift 1911, No. 35.

Werner, Therapeutische Monatshefte 1911, p. 167. — Compare A. Plehn, Therapie und Prophylaxe der Malariarückfälle, Therapie der Gegenwart 1911, p. 531.

of quinine prescribed is readily soluble in water, like quinine hydrochloride, or soluble with difficulty, like pure quinine or the tannate. The author fixes the dose for internal administration for adults at 0.8 gramme (12 grains) of pure quinine a day, and the quantity of quinine salt corresponding to this amount, for example 1 gramme (15 grains) of quinine hydrochloride. For children he reckons 0.1 gramme ( $1\frac{1}{2}$  grains) for the first year, and 0.1 gramme ( $1\frac{1}{2}$  grains) for every further year up to 10 years, and places the total daily dose at 1 gramme (15 grains) of quinine hydrochloride.

The time for administering the drug is chosen so as to fall about 6 hours before the sporulation of the parasites, which can, according to the author, be easily reckoned from the temperature curve in tertian and quartan malaria. But in tropical malaria and in recurrences it is a matter of great difficulty to fix the correct time for administering the quinine, and it is therefore necessary, either to wait until the temperature has dropped to  $37^{\circ}$  C. and then give 1 gramme (15 grains) of quinine hydrochloride, or better still, to follow the method of Nocht and give 0.2 gramme (3 grains) of quinine hydrochloride at intervals of two hours 5 times a day. By this method the by-effects of the quinine medication and the blackwater fever are pushed more into the background, and the employment of quinine can be started earlier. The administration of 0.2 gramme (3 grains) of quinine hydrochloride 5 times daily should be continued for a week, even though after 2 to 3 days the asexual parasites have disappeared from the peripheral blood and the fever has abated, for in this way recurrences are avoided. For this purpose the patients must continue to take quinine for 2 to 3 months, even if they are feeling quite well at the end of the week's treatment; it should be taken for two consecutive days, then an interval allowed and again taken for two days and so on, the interval being lengthened each time. The quinine is best taken internally, unless this is rendered impossible on account of difficulty in swallowing, as is the case in the severest comatose forms of malaria. In these cases the quinine is given intravenously in saline infusions. Werner recommends for this purpose a solution of 1.5 grammes (24 grains) of urethane quinine\*) in 200 c. c. ( $6\frac{2}{3}$  oz) of normal saline solution, which

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\*) Compare Merck's Report 1908, p. 284.

is said to have a prompt antiparasitic action. The subcutaneous and intramuscular injections are said to be less satisfactory.

A communication of Ph. Kopanaris is of interest, according to which quinine proved far superior to atoxyl and salvarsan in the malaria of birds. It has no prophylactic, but only a curative action, if given by intramuscular injection in 0.5 p. c. solution.

A phenomenon which still requires confirmation, and which will then be of importance in quinine treatment, has been observed by de Sandro. In his pharmacological investigations on dogs, quinine appeared to have an inhibitory action on the new formation of blood. The author discovered this property of quinine after venesections. In animals which were under the influence of quinine, the formation of hæmoglobin and erythrocytes in the blood took place more slowly than in animals which had not received quinine. It is also said to make no difference whether the animals had been treated with quinine beforehand, or whether they were given the preparation at the time of the venesection.

Infusions of a 0.1 to 0.3 p. c. solution of quinine sulphate are, according to Bruckner, said to have an excellent action in cholera, typhoid fever, dysentery and trichinosis. Even though it cannot be denied that mercury salts are more effective, yet quinine has a sufficiently powerful bactericidal action on pathogenic bacteria and aids in the destruction of toxins. In whooping-cough, also, the rectal application of quinine is useful. It was even found of service in several cases in which the administration of euquinine by mouth had been without effect. 1 gramme (15 grains) of quinine sulphate, together with the amount of dilute sulphuric acid necessary to effect solution, is dissolved in 150 grammes (5 oz) of water, and one tablespoonful of this is added to the quantity of warm water needed for an enema. The application is repeated twice daily. Further, the author has successfully used infusions of quinine with aloes for oxyuris vermicularis. For this purpose he employed a solution of 2 grammes (30 grains) of quinine sulphate in 150 grammes (5 oz) of water acidified with sulphuric acid, to which he added 5 grammes

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Kopanaris, Archiv für Schiffs- und Tropenhygiene 1911, No. 18.  
Sandro, Riforma medica 1911, No. 16 and 18.

Bruckner, Revue médico-pharmaceutique 1911, No. 1, p. 5. (Constantinople.)

(90 min.) of tincture of aloes. For an enema one tablespoonful of this is added to the necessary quantity of water.

R. Marek investigated the action of quinine in strengthening labour pains and was able to confirm this property of the drug. But the action is very uncertain and it can never be foreseen whether or not it will take place in a particular case. Neither the length of time of the labour nor its course, nor the course of previous labours, nor the number of pregnancies, nor yet the age of the mother form a standard for its action. The author was only able to confirm one fact, viz., that quinine acts less well in primiparæ, and that in multiparæ, in whom it had not acted in former labours, it was later never successful. Further, it has no action if the muscles of the uterus have been stretched for a prolonged period.

E. Schepelmann considers quinine, when combined with antipyrin, to be a useful local anæsthetic for endodermic and hypodermic use. Its injection causes a burning pain lasting for a short time, but the action of the drug is immediate and lasts for hours. The addition of antipyrin and adrenalin is said to abolish more or less the painfulness of the quinine injections. The author prescribed a solution of 0.3 gramme (5 grains) of quinine hydrochloride and 0.3 gramme (5 grains) of antipyrin in 10 grammes ( $\frac{1}{3}$  oz) of water, of which he injected a quarter to two syringefuls according to the extent of the operation area. A solution of 0.3 gramme (5 grains) of quinine hydrochloride and 0.0005 gramme ( $\frac{1}{125}$  grain) of adrenalin in 10 c. c. ( $\frac{1}{3}$  oz) of water may also be used.

### Quinine Guaiacol-Sulphonate.

Quinine orthoguaiacol-sulphonate,  $C_{20}H_{24}N_2O_2 \cdot C_6H_3(OH)(OCH_3)SO_3H$ , according to Horand, forms small, yellowish crystalline plates, which are distinguished from other quinine salts by their ready solubility in water. It dissolves with difficulty in alcohol, ether and chloroform. Corresponding to its components, quinine and guaiacol-sulphonic acid, the preparation acts as a powerful antiseptic which renders it a useful drug in a number of infective diseases, such as in-

Marek, Wiener medizinische Wochenschrift 1911, No. 34.

Schepelmann, Therapie der Gegenwart 1911, No. 12.

Horand, Lyon médical 1911, No. 16. — Klinisch-therapeutische Wochenschrift 1911, p. 553.

fluenza, typhoid fever, tuberculosis, acute rheumatic arthritis, syphilis, cancer, malaria, and also in neurasthenia, diabetes, pertussis, struma and trigeminal neuralgia. Its absorption is said to take place rapidly on account of its ready solubility in water, and with healthy kidneys quinine is said frequently to appear in the urine in 20 minutes. The maximum amount of elimination takes place in about 5 to 6 hours. The preparation is administered internally in daily doses up to 4 grammes (60 grains) rectally in the form of suppositories containing 0.1 to 0.4 gramme ( $1\frac{1}{2}$ –6 grains), and subcutaneously in doses up to 0.5 gramme ( $7\frac{1}{2}$  grains) dissolved in 2 c.c. (34 min.) of water. The subcutaneous injection of large doses causes transitory symptoms of intoxication, such as giddiness, headache, deafness, irregular and rapid pulse and slowing of the respiration.

### Ragit.

The utility of Marx's dry nutrient medium (ragit agar, ragit broth, and Endo-tablets) was, following Sparmberg and Amako, made the subject of exhaustive investigation by R. Müller. In agreement with these authors, he confirmed the fact that the growth of bacterial colonies on ragit agar is practically the same as on the ordinary agar nutrient medium. Endo-tablets are even superior to Endo-agar. Marx's ragit nutrient media are therefore, according to the author, excellently suited for use in small laboratories, in travelling and war laboratories, more especially because the dry preparations only take up very little room in the portable bacteriological cases.

K. Poppe came to the same favourable conclusion as to the utility of the ragit nutrient media, and he also emphasises the simple and rapid method of preparation of these nutrient media. He compared the growth of certain bacteria on ordinary agar and in ordinary nutrient broth with that on the corresponding ragit preparations and found that the so-called typhoid-coli group grow just as luxuriantly on ragit agar and in ragit broth as on the corresponding nutrient media in ordinary use. Indol was formed by *Bacillus coli* in ragit broth to

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Sparmberg-Amako, Merck's Report 1910, p. 299.

Müller, Dissertation, Leipzig 1911.

Poppe, Berliner tierärztliche Wochenschrift 1911, No. 33.

the same degree as in slightly alkaline nutrient broth. The ordinary pigment-forming micrococci and also bacillus proteus, bacillus subtilis and other bacilli grew well on ragit agar, and the former also gave rise to plentiful pigment formation. The bacillus of swine fever did not grow on ragit nutrient media, whereas the chicken cholera bacillus, related to it, grew more luxuriantly on ragit agar than on ordinary agar. The bacillus of erysipelas grew poorly on ragit agar and only gave rise to faint cloudiness in ragit broth.

For the isolation of the bacteria of the typhoid-coli group, in the author's experience, a fuchsin agar, prepared with the help of Endo-tablets from ragit agar is very useful; bacillus coli especially is said to form strongly fluorescent colonies on this nutrient medium. In order to avoid the intense red coloration one tablet may be used for the double amount of ragit agar (200 c.c.), for luxuriant growth also takes place under these conditions. Ragit agar can also be used for the preparation of litmus-milk-sugar-agar and of Löffler's Malachite green agar.

### Reagents.

Methylglyoxal, as a test for phenols, alkaloids, etc., is, according to Denigès, prepared as follows: 0.6 c.c. of bromine is dissolved in 100 c.c. of water, a mixture of 2 grammes of glycerin and 18 grammes of water is added, this is warmed for 2 minutes on a water-bath and then boiled for 5 to 6 minutes until the excess of bromine has been driven off. When it is cool, 20 c.c. of sulphuric acid are added and 50 c.c. are distilled off. This distillate constitutes the reagent. It is used in combination with sulphuric acid, or with sulphuric acid and potassium bromide.

Salicylic acid in concentrated sulphuric acid (1 to 5:100) is used by Caron and Raquet as a test for nitrates in water. For this purpose the water to be examined is evaporated to dryness, first 1 c.c. of the reagent and then 10 c.c. of distilled water and 10 c.c. of liquid ammonia are added. In the presence of nitrates a yellow solution results, which may also be estimated colorimetrically. For this test it is imperative to prepare the reagent each time before use.

Denigès, Bulletin des travaux de la société de pharmacie de Bordeaux, Vol. 49, p. 196.

Caron-Raquet, Répertoire de pharmacie 1911, p. 245.

Ferric chloride-acetic acid (1:1000) is used by Kollo for the identification of herniaria extract. The aqueous solution of the extract, to which a few drops of ammonia have been added, is shaken up with ether, the ether is evaporated and the yellow residue dissolved in 3 c.c. of iron chloride-acetic acid. The solution is carefully "layered" over concentrated sulphuric acid. At the junction of the two fluids a brown zone is first formed and over it a yellowish-brown fluid. By reflected light a second zone of a very beautiful violet colour may be seen under the brown zone; this gradually transfuses into the colourless sulphuric acid and gradually colours it violet. The appearance of the colour is very constant. A solution of 0.05 gramme of herniaria extract in 10 grammes of water is said to give a definite reaction.

Resorcin in alkaline solution is suggested by J. Abelin as a reagent for salvarsan in the urine. About 8 c.c. of the urine to be tested are acidified with 5 to 6 drops of dilute hydrochloric acid and 3 to 4 drops of a 0.5 p.c. aqueous solution of sodium nitrite are added. A few drops of this mixture are added to 6 c.c. of the colourless alkaline resorcin solution, which in the presence of salvarsan immediately assumes a distinct red colour. The reaction only takes place if the mixture remains alkaline. P. Beisele doubted the specificity of this test.

Sodium nitrite solution (1:2000) is, according to Barberio, a simple and reliable test for indican in the urine. If 5 c.c. of urine containing indican are added to 3 drops of the reagent, 2 c.c. of chloroform and 5 c.c. of concentrated hydrochloric acid, the mixture is coloured violet. On gently shaking, the chloroform turns blue, while the aqueous fluid remains yellow, red or violet according to the amount of indican present.

### Resorcin.

If in the treatment of verrucæ planæ juveniles the use of arsenic, which is generally successful, should fail, the warts,

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Kollo, Pharmazeutische Praxis 1911, p. 293.

Abelin, Münchener medizinische Wochenschrift 1911, p. 1002 and 1566.

Beisele, Münchener medizinische Wochenschrift 1911, p. 1313.

Barberio, Policlinico 1911, 23<sup>rd</sup> April. — Münchener medizinische Wochenschrift 1911, p. 1838.

according to E. Saalfeld's suggestion, may be treated twice daily with the following liniment: Rp. Resorcin 5.0 grammes (75 grains), Spirit. sapon. kal. ad 50.0 gramme (2 oz). This causes a gradual reduction in size and finally the disappearance of the warts. In obese individuals this treatment is also preferable to the administration of arsenic, which promotes the deposition of fat.

In chronic conjunctivitis Knapp considers it advantageous to use a 2 to 3 p.c. aqueous solution of resorcin in the place of resorcin ointments. The solution may be instilled 3 times a day. The resorcin solution will keep better if a boric acid solution is used instead of plain water.

As a test for callus, Tswett uses a solution of 1 gramme of resorcin in 100 c.c. of water, which is rendered alkaline by the addition of 0.1 c.c. of liquid ammonia and is left to oxidise spontaneously in the presence of air. It assumes a deep blue coloration. The colouring matter, named by the author "resoblue", keeps for months. It colours the callus of the sieve-tubes an intense blue, while cellulose remains unstained. Alone or in combination with other stains the reagent is useful for microscopic work in botanical investigations. Thus, for example, with a mixture of resoblue and Congo red callus can be stained blue and cellulose red. In concentrated potassium acetate solution and Canada balsam the resoblue colour is permanent.

### Ristin.

The mono-benzoic acid ester of ethylene glycoll, ( $C_6H_5COO \cdot CH_2 \cdot CH_2 \cdot OH$ ), has recently been recommended as a cure for scabies. It forms a crystalline mass with a faintly aromatic smell, melting at  $46^\circ C$ . Boiling point  $165^\circ C$ . (12 mm. pressure). The preparation is almost insoluble in water, but readily soluble in alcohol, ether, benzol, chloroform and fatty oils. The 25 p.c. solution of the ester in alcohol and glycerin is put on the market under the name of "ristin".

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Saalfeld, Medizinische Klinik 1911, p. 1938.

Knapp, The Hospital 1911, January. — Revue de thérapeutique 1911, p. 634.

Tswett, Comptes rendus de l'académie des sciences 1911, Vol. 153, p. 503.

So far, J. Neuberger and C. Tollens have expressed a very favourable opinion as to the therapeutic value of ristin. Neuberger treated 85 cases of scabies with it and found that it was always well borne. Usually 3 applications, each of 50 grammes ( $1\frac{2}{3}$  oz) of ristin, sufficed and only in very extensive cases may a fourth application at the principal sites of localisation be advisable. As the 3 applications can be made in one day, treatment with ristin does not take longer than do other forms of treatment. The irritation was diminished after the first application and disappeared altogether after the second or third. The author observed no recurrences. Tollens experienced equally good results. He states that the mites are usually killed by the first application and certainly after the second or third. Apart from the effectiveness of the drug, both authors emphasise its harmlessness and absence from irritant properties, and point out that it is free from smell and cleanly in use.

### Sabadilla.

For the destruction of the mites in sarcoptes scabies of horses, mixtures have long been used which contain benzine, chloroform, turpentine oil, petroleum, etc., preparations which take effect slowly, do not act sufficiently on the eggs of the parasites and cause cutaneous irritation. According to Boudéaud, an old-fashioned prescription of sabadilla seeds combined with sulphur and alum is decidedly more effective. The prescription is:

Rp. Sem. sabadill. pulv.	100.0 grammes ( $3\frac{1}{3}$ oz)
Sulphur. sublim.	60.0 grammes (2 oz)
Alum. usti pulv.	40.0 grammes ( $1\frac{1}{3}$ oz)
Ol. Oliv.	1000 c.c. ( $33\frac{1}{3}$ oz)

In order that the sabadilla seeds may be thoroughly extracted, the mixture is allowed to digest for at least an hour with constant stirring. The diseased animals are cleansed by means of soap and are then treated with the medicament at suitable intervals; it is rubbed into only half the body

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Neuberger, Münchener medizinische Wochenschrift 1911, p. 2220.

— Compare Pharmazeutische Zeitung 1911, p. 776.

Tollens, Deutsche medizinische Wochenschrift 1911, p. 2040.

Boudeaud, Revue générale de médecine vétérinaire 1911, 13<sup>th</sup> January.

at a time and the body is thoroughly cleansed with soap before every repetition of the application. This treatment is said to cure the most obstinate cases of sarcoptes scabies in a short time, without the least cutaneous irritation.

### Salophen.

This salicylic preparation\*), which was introduced into therapeutics in 1891, has been made the subject of a careful therapeutic investigation by G. Buccelli. Especially in influenza, and in the symptoms and complications accompanying it, the author has used it successfully in combination with other recognised drugs. In simple influenza he obtained a prompt action and decreased the duration of the attack by giving an average daily dose of 3.5 to 4 grammes (52—60 grains). The following prescription also proved useful:

Rp. Salophen 0.75—1.0 gramme (12—15 grains)  
Quinin. hydrochlor. 0.15—0.25 gramme ( $2\frac{1}{3}$ —4 grains)  
M. Ft. pulv. Mitte XII. Sig.: One powder to be taken  
4 times a day.

Salophen also proved of service in the complications of influenza, diffuse bronchitis, broncho-pneumonia, polyarthritis, etc., and in children's diseases. In acute polyserositis and rheumatic chorea, and in sciatica he prescribed:

Rp. Salophen.  
Aspirin. aa 0.5 gramme ( $7\frac{1}{2}$  grains)  
Quinin. salicyl. 0.15 gramme ( $2\frac{1}{3}$  grains)  
Caffein. 0.05 gramme ( $\frac{3}{4}$  grains)  
M. Ft. pulv. Mitte XII. Sig.: One powder to be given  
4 to 6 times a day.

For neuritis, migraine, facial and intercostal neuralgia he recommends:

Rp. Salophen. 0.75 gramme (12 grains)  
Phenacetin. 0.25 gramme (4 grains)  
Quinin. valerian. 0.1 gramme ( $1\frac{1}{2}$  grains)  
M. Ft. pulv. Mitte XV. Sig.: One powder to be taken  
5 times a day.

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\*) Compare Merck's Reports 1891 and 1904.

Buccelli, Archivio di farmacologia sperimentale e scienze affini 1911, 15<sup>th</sup> April.

Rp. Salophen.	0.75 gramme (12 grains)
Aspirin.	0.75 gramme (12 grains)
Caffein.	0.05 gramme ( $\frac{3}{4}$ grain)
M. Ft. pulv. Mitte X.	Sig.: One powder to be taken 3 to 5 times a day.

Buccelli considers salophen an effective and harmless drug, which is not contra-indicated in nephritis and albuminuria.

### Salvarsan.

No preparation which has led to such abundant exchange of experiences and opinions in the literature as salvarsan\*) has previously been introduced into therapeutics. It would therefore be a bold undertaking to attempt to give a really impartial presentation of all the "for and against", the benefit and harm to be derived from salvarsan treatment, especially as for anyone not actually engaged in salvarsan research an unprejudiced review of the material which has mounted up in literature would present great difficulties. But so much is certain, that the aim of the great scientist, the "therapia sterilisans magna", has not been entirely fulfilled by salvarsan. On the other hand, it must be acknowledged that the new remedy has already accomplished much and will probably accomplish still more, even though it be not a panacea for all diseases due to spirochetes. Syphilis was the disease in which too much was at first promised from salvarsan treatment and for this reason the results have sometimes led to disappointment. This is not so much the fault of salvarsan itself, as of the exaggerated expectations which were attached to this remedy.

Salvarsan is undoubtedly of most use in primary syphilis, in which either alone or combined with mercury it is said to bring about a cure in about 90 p. c. of the cases. But in secondary and tertiary syphilis it will be advisable to use preparations of mercury and iodine besides salvarsan. Other diseases besides syphilis which are difficult to influence are leprosy, pemphigus and trypanosome diseases, such as sleeping sickness and kala-azar, while the prospects are very good in tertian malaria, relapsing fever, frambæsia, Aleppo boil, bilharzia, and in veterinary medicine in epizootic lymphangitis and chronic glanders.

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\*) Compare Merck's Report 1910.

With regard to the method of application of salvarsan, intravenous injection is most in vogue, while the subcutaneous and intramuscular employment of aqueous solutions has been relegated to the background on account of the troublesome symptoms to which they give rise. Intravenous injection is certainly the simplest and most convenient form and is followed by rapid action, while subcutaneous and intramuscular injections are only specially suitable when the establishment of a depot is desirable, e. g., chronic treatment. For intravenous injection the use of neutral salvarsan solutions\*) is to be preferred, for subcutaneous and intramuscular use suspensions of the drug in paraffin, olive oil or iodipin. Among these the so-called "Ioha", a 40 p. c. emulsion of salvarsan in iodipin, deserves special mention, as, according to Schindler, it has various advantages over other oily emulsions. One advantage of emulsions is that the mass to be injected is ready for the doctor's use, since stable preparations of this kind can be issued ready for use.

A discussion of the secondary effects occupies a considerable space in the literature of salvarsan; they have been frequently observed, and besides local symptoms of irritation, consist chiefly of fever, headache, vomiting, diarrhoea, and occasionally of nerve-paralysis, arsenic zoster, injuries to the eyes, icterus, nephritis, etc. According to Wechselmann, the majority of these symptoms can be traced to the use of water containing bacteria, an observation which has recently led to special attention being paid to the purity of the water used in the preparation of salvarsan solutions. Other secondary effects, and the fatal cases which have been recorded, are considered to have been due to faulty technique.

As for obvious reasons it is impossible to refer here to the many hundreds of publications which appeared in the course of the last year, and as on the other hand an exception cannot and shall not be made to my custom of enumerating in my Annual Report the more important international literature, the salvarsan literature of 1911 will be given below for those interested in as clear and comprehensive a form as possible. I have sought to attain this end by arranging the publications

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\*) With regard to the preparation and dosage of the salvarsan solutions, the prospectuses on the subject should be consulted.

alphabetically according to indications, secondary effects, fatal cases, technique, and authors.

**Anæmia (pernicious):**

Bramwell, Brit. Med. Journ. 1911, p. 546. — Leede, Münch. med. Woch. 1911, No. 22.

**Angina, Scurvy:**

Achard-Flandin, Bull. méd. 1911, p. 385. — Gerber, Arch. f. Laryngol., Vol. 24, No. 3. — Tuschinsky, Münch. med. Woch. 1911, No. 50.

**Antibody-Formation:**

Friedberger, Therap. Monatshefte 1911, No. 5.

**Banti's Disease:**

Schmidt, Münch. med. Woch. 1911, No. 12.

**Bilharzia:**

Johannidès, Deutsche med. Woch. 1911, No. 34.

**Cancer:**

Czerny, Münch. med. Woch. 1911, No. 36.

**Chorea minor:**

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#### Quantitative Estimation:

Gaebel, Archiv der Pharmazie 1911, p. 241.

#### Santonin.

According to French authors, the glycosuria of diabetics can be successfully treated and even completely cured by means of santonin\*), and recently the so-called Séjournet pills (each containing 0.02 gramme [ $\frac{1}{3}$  grain] of santonin) have been specially recommended for this purpose. These statements led G. Walterhöfer to test the value of santonin in diabetes. His investigations gave negative results. In not a single case did the administration of 3 doses daily of 0.025 gramme ( $\frac{2}{5}$  grain) of santonin lead to the disappearance of the sugar. In two cases it was not even found possible, without altering the diet, to lessen the amount of glycosuria or even to raise the limit of tolerance for carbohydrates. In two other cases a favourable influence on the elimination of sugar could not be denied but this influence was very transitory, and after inter-

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\*) Compare de Grissac, Scalpel 1906, p. 246. — Merck's Report 1906, p. 213.

Walterhöfer, Berliner klinische Wochenschrift 1911, p. 421.

rupting the medication, the renewed administration of santonin did not have the same effect. Walterhöfer seeks to explain the good effect observed by other authors to follow the employment of santonin by the fact that with this medication a substance (stained red by caustic potash) appears in the urine; it is lævo-rotatory and has not yet been chemically defined. In his opinion, this causes the estimation of the sugar present to yield too low a content when carried out polarimetrically. These conclusions make the value of santonin in diabetes mellitus appear very questionable.

### Santyl.

W. Mehlhorn tested santyl\*) on about 250 patients in the course of 3 years and obtained very satisfactory results with this remedy for gonorrhœa. It was always well taken on account of its slight taste, and in every case proved to be absolutely non-irritant, and displayed an excellent action. Even sensitive patients never complained of gastric or renal trouble if the drug were taken after meals. It very rarely failed to act, but occasionally did so in a very hysterical patient, whose bladder trouble at first disappeared immediately, but in whom new nervous troubles appeared at a later date. But in this case all other medicaments failed.

Santyl is indicated in urethritis, cystitis, caruncles of the urethra, dysuria, tenesmus of the bladder, which has originated partly from inflammatory affections of the mucous membrane and partly from a reflex nervous condition, in periodic bladder troubles occurring during the menses, strangury in a neurosthenic subject, etc.

In cystitis it is well to combine the use of santyl with infusion of bearberry leaves and to prescribe a suitable diet. In a few cases of chronic suppurative cystitis and of carcinoma which had invaded the bladder, the administration of santyl almost immediately caused the urine to become clear, while the previous prolonged administration of urotropine did not have this effect. Besides the santyl medication, irrigation of the bladder was carried out. In vaginal operations, in which more or less extensive blunt separation of the bladder was necessary and in which slight bladder disturbances ap-

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Mehlhorn, Zentralblatt für die gesamte Therapie 1911, p. 396.

\*) Compare Merck's Reports 1905—1910.

peared during the first few days, the administration of santyl caused their rapid disappearance.

Mehlhorn considers the simplest method for prescribing santyl to be in the form of drops. 25 drops are given 3 times a day after food in water or with caster-sugar, or 2 santyl capsules (0.4 gramme each) 3 times a day. The author no longer uses santyl tablets as, in his experience, they do not act so well.

### Scarlet Red.

Scarlet red\*), as is well known, was used with good results by Schmieden and Morawetz for ulcers of the leg. Wehner uses for this purpose not the 8 p.c. ointment, as this often gives rise to irritation, so that erosions or even ulcers appear between the newly formed epithelial islands, but a 4 p.c. ointment prepared according to the following prescription: Rp. Scarlet red 4.0 granimes (60 grains) tere cum chloroformio q. s., Ung. lenicet ad 100.0 grammes ( $3\frac{1}{3}$  oz). This can be used without fear for 3 days. V. Pavia also found that in the after treatment of radical operations on the middle-ear the 8 p.c. ointment gives rise to irritation and he therefore uses the drug in powder form. He prescribes: Rp. Scarlet red 1.0 gramme (15 grains), Acid. boric. pulv. 9.0 grammes (135 grains). After cleansing the cavity with cotton wool and cauterising any exuberant granulations which may be present, this powder is insufflated and a loose, sterile strip of gauze is introduced. This procedure is at first repeated daily and later every two, three, or four days. The results are said to be very good. It appears from a publication by O. Sachs that the action of forming epithelium is not peculiar to scarlet red and amido-azotoluol\*\*), but is also shared by other aniline dyes, such as brilliant red, madder lake, light-yellow and green lake.

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\*) Compare Merck's Reports 1908—1910.

Schmieden, Zentralblatt für Chirurgie 1908, No. 6.

Morawetz, Therapeutische Monatshefte 1909, p. 479.

Wehner, Deutsche medizinische Wochenschrift 1911, p. 1081.

Pavia, Therapie der Gegenwart 1911, p. 47.

Sachs, Wiener klinische Wochenschrift 1911, p. 1551.

\*\*) Compare p. 146.

### Scopolamine Hydrobromide.

The communications on the employment of scopolamine in combination with morphine for the induction of, or as a supplement to, anæsthesia before operations, which have been published by B. Korff, R. Hastrup, F. Rood, A. Grigorjan, Brüstlein, Eckert, W. Brant, G. Neuber, R. von Hippel, and others, confirm the statements given in sufficient detail in my Reports\*) during the past years. Therefore only the method of using scopolamine will be briefly recalled to memory.

In operations lasting for a long time, such as laparotomies and operations on the joints, in which anæsthesia is to be maintained by ether or chloroform, Korff considers it best to inject 0.0004 gramme of scopolamine hydrobromide and 0.01 gramme of morphine hydrochloride one and a half hours and half an hour before the beginning of the operation. If the scopolamine-morphine is to be the chief anæsthetic, only supplemented by a little ether if necessary, 0.0012 gramme of scopolamine hydrobromide and 0.03 gramme of morphine hydrochloride are given, divided into 3 injections. Grigorjan found that for the induction of anæsthesia with scopolamine-morphine, injections of 0.0002 gramme of scopolamine hydrobromide were sufficient. In judging whether or not a patient may safely be subjected to scopolamine-morphine anæsthesia, according to recent views, it is not so much the age as the bodily constitution of the patient upon which the decision must be based. Thus Neuber administers to robust patients varying in age from 20 to 70 years a total amount of 0.0008 gramme of scopolamine hydrobromide and 0.02 gramme of morphine hydrochloride, or 12 divisions of scopomorphine, while to weak patients he only gives a total injection of 0.0005 gramme of scopolamine hydrobromide and 0.0125 gramme of morphine hydrochloride, or 7.5 divisions of scopomorphine.

Korff, *Medizinische Klinik* 1911, No. 2.

Hastrup, *Ugeskrift for Læger* 1911, No. 1 and 2.

Rood, *British Medical Journal* 1911, II, p. 652.

Grigorjan, *Wratschebnaja Gaceta* 1911, No. 31.

Brüstlein, *Zentralblatt für Chirurgie* 1911, p. 345.

Eckert, *Zentralblatt für Chirurgie* 1911, p. 857.

Brant, *Russkij Wratsch* 1911, No. 13.

Neuber, *Zeitschrift für ärztliche Fortbildung* 1911, No. 12.

Hippel, *Fortschritte der Medizin* 1911, p. 229.

\*) Compare Merck's Reports 1902—1910.

For persons between 6 and 20 years of age he prescribes, according to age, altogether 4 to 12 divisions of scopomorphine.

Rood recommends the following combination of scopolamine, atropine and morphine. Men are given an injection of 0.01 gramme of morphine an hour and a half before the operation and three-quarters of an hour later 0.0006 gramme of scopolamine hydrobromide, 0.0005 gramme of atropine sulphate and 0.01 gramme of morphine tartrate. Women were not given the first injection of morphine, but received the injection of scopolamine-atropine-morphine mentioned above three-quarters of an hour before the operation. Children aged 10 to 16 were given 0.0006 gramme of scopolamine hydrobromide, 0.0006 gramme of atropine sulphate and 0.0075 gramme of morphine tartrate. The author used ether as an anæsthetic. The advantage of using atropine is said to lie in the absence of salivation and diminished liability to pneumonia.

The experiences which have been collected with regard to the employment of scopolamine-morphine in bringing about a semi-unconscious state during labour sound most satisfactory. Among others, B. Bosse reports in detail upon this subject. The employment of the drug will always give good results so long as Dietschky's condition be adhered to: The pains must occur at regular intervals, must be strong and must be painful to the parturient woman. Care is necessary in weakly persons, in the presence of high temperature, in uncompensated heart disease and in displacement of the heart (kypho-scoliosis) with considerable respiratory trouble. Primary inertia forms an absolute contra-indication; in secondary inertia individualisation is necessary. In the author's opinion, this method of producing unconsciousness may be safely used by the general practitioner after a little practice, provided he pays attention to the work which has been done and also considers each case on its own merits. Like Cremer, so Bosse considers it absolutely essential in bringing about the semi-unconscious state to use Merck's scopolamine hydrobromide, which is free from poisonous constituents. Further, tablets and commercial scopolamine-morphine solutions should not be employed, but the scopolamine-morphine solution *should always be freshly prepared*. Bosse, therefore, never injects a solution which is older than 24

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Bosse, Berliner Klinik 1911, No. 272.

Dietschky, Korrespondenzblatt für Schweizer Aerzte 1908, No. 15.

hours. Every gramme of the solution should contain 0.0003 gramme of scopolamine hydrobromide and 0.01 gramme of morphine hydrochloride. The author did not administer the first syringeful until there were distinct pains which were painful and followed one another in regular sequence, at the earliest when the os was the size of a sixpenny piece; he generally gave the second injection 50 minutes later, but he only gave a third if necessary  $2\frac{1}{2}$  to 3 hours later, and then only half a syringeful. In protracted labour 0.5 gramme of the solution was injected every 3—4—5 hours, as soon as the pains began to be burdensome. The necessary number of syringefuls was on the average  $2\frac{1}{5}$ , generally 1 to 3 and only in exceptional cases 4 to 6 syringefuls were required, and the average interval between the separate injections was 3 hours 10 minutes. In every case, whether it had been necessary to keep up the unconscious state for long or if a specially large number of injections had been required, the mother's condition did not once give rise to anxiety. Bosse's total results may be considered very satisfactory in that, according to his reckoning, he obtained complete or almost complete amnesia in 80 p.c. of his cases.

As regards the occurrence of asphyxia and respiratory apoplexy which have been observed for some time, the degree of asphyxia, according to Bosse, does not in the least depend upon the unconscious state, but upon the duration of the expulsive stage. The author has never seen a delayed action of scopolamine on the children. Klauber, who would also be sorry to dispense with scopolamine, demands that the drug should not be discredited, but that rather the conditions should be investigated to which the appearance of respiratory apoplexy may be due. Thus he considers that disturbances of the respiratory organs are always a contraindication to the employment of scopolamine. Although scopolamine appears to have such a beneficial action in preventing pulmonary complications when the respiratory apparatus is intact, it appears to be equally dangerous to a respiratory system incapable of response.

A favourable opinion on the value of scopolamine-morphine in midwifery has also been expressed by Gauss, Free-

land and Salomons, P. Strassmann, Th. N. Iljin, W. Tichauer and D. Corbett.

As a substitute for morphine in scopolamine anæsthesia, pantopon (omnophon) was suggested by J. R. Häni, von Deschwanden, M. von Brunn, G. Brüstlein, Johannsen, A. Zeller, F. Eckert, H. Fowelin, L. Simon, Zahradnicky, C. Haeberlin, F. Heinsius, Gray, E. Aulhorn and Kolde. The dose of scopolamine suggested by the various authors is the usual one which has been mentioned above; the dose of pantopon (omnophon) is 0.01 to 0.04 gramme. The technique and the combination with inhalation anæsthesia is the same as for scopolamine-morphine anæsthesia.

## Sera and Antigens.

### Antithyroidin Moebius.

The communications on the value of antithyroidin in the treatment of thyrotoxic symptoms are all most favourable\*). Thus E. Laser describes 4 cases of Graves' disease, in which this medicament proved most useful. In 3 cases the pulse rate fell in consequence of antithyroidin medication and remained considerably lower than before, either permanently or for a

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Freeland-Solomons, British Medical Journal 1911, I, p. 187.

Strassmann, Berliner klinische Wochenschrift 1911, No. 23.

Iljin, Russkij Wratsch 1911, No. 12.

Tichauer, Dissertation Freiburg 1911.

Corbett, British Medical Journal 1911, I, p. 868.

Häni, Therapie der Gegenwart 1911, No. 2.

Deschwanden, Korrespondenzblatt für Schweizer Ärzte 1911, No. 4.

Brunn, Zentralblatt für Chirurgie 1911, No. 3.

Brüstlein, Zentralblatt für Chirurgie 1911, No. 10.

Johannsen, Zentralblatt für Gynäkologie 1911, No. 19.

Zeller, Münchener medizinische Wochenschrift 1911, No. 25.

Eckert, Zentralblatt für Chirurgie 1911, No. 25.

Fowelin, Zentralblatt für Chirurgie 1911, No. 27.

Simon, Münchener medizinische Wochenschrift 1911, No. 32.

Zahradnicky, Zentralblatt für Chirurgie 1911, No. 30.

Haeberlin, Münchener medizinische Wochenschrift 1911, No. 33.

Heinsius, Berliner klinische Wochenschrift 1911, No. 41.

Gray, Lancet 1911, 2<sup>nd</sup> September.

Aulhorn, Münchener medizinische Wochenschrift 1911, No. 12.

Kolde, Münchener medizinische Wochenschrift 1911, No. 28.

\*) Compare Merck's Reports 1902—1910.

Laser, Münchener medizinische Wochenschrift 1911, p. 689.

long time. In 2 cases the apex-beat, which had been displaced, slowly returned to the nipple-line and thus gave a further sure sign of more tranquil cardiac action; or it may even be justifiable to draw the conclusion that a dilated heart has returned to normal as a result of the treatment. The circumference of the neck was visibly decreased in 2 cases. In all 4 patients a considerable improvement in the subjective condition was unmistakable. The certain, practically specific action of the drug also constitutes a proof that the different morbid conditions are caused by increased activity of the thyroid gland. In one case, certainly, the general treatment given at first had been quite effective, but this, according to the author, is much more difficult to carry out than the simple prescription of antithyroidin.

As reported by A. Krecke, the cardiac conditions accompanying thyroidism, treated by him with antithyroidin, were benefited as much as in Graves' disease. In cardiac lesions, of course, no action can be expected. Thus the drug may occasionally assist in differential diagnosis.

The excellent action of antithyroidin combined with balneotherapy, as was formerly described by various authors, Alexander among others, has been fully confirmed by P. Stein. In a few cases he was able to convince himself that Nauheim baths were beneficial in Graves' disease, but in no case did he observe such striking results from the baths alone as with the combined use of the baths and the employment of antithyroidin. As regards the dosage of the preparation, according to Stein, no definite dose is quoted in the literature. He himself recommends the administration of 10 drops at first in the morning and afternoon, and if the patient is excited at night this dose is repeated, and the amount is increased slowly by 2 to 6 drops a day and continued until at least 30 drops are taken twice a day. If by that time no action is apparent, the dose may be slowly increased without fear of cumulative action until the desired effect is attained. E. Fernandez Sanz also found that

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Krecke, *Münchener medizinische Wochenschrift* 1911, No. 30 and 31.

Alexander, *Münchener medizinische Wochenschrift* 1905, p. 1393.  
Stein, *Zeitschrift für Balneologie* 1911, No. 14.

Sanz, *Semana medica* (Buenos Ayres) 1910, 1<sup>st</sup> December. —  
*Revue de thérapeutique* 1911, p. 164.

a beneficial action is not always obtained with small doses, for the amount of toxin to be neutralised in individual cases of Graves' disease may vary within wide limits; in one case he only obtained a beneficial result after the administration of large doses of the preparation. For benign cases of Graves' disease the author recommends rest, hydrotherapy and antithyroidin, while in acute, rapidly progressive cases he is in favour of operation.

The results of treatment of so-called iodine-Graves' disease with antithyroidin are also of therapeutic interest; this is a condition in which symptoms of Graves' disease appear in specially predisposed persons after the administration of iodine. Römheld obtained a distinct improvement by serum treatment. His observations agree with Konried's experiences, who gave it with good results for iodine fever.

Further, antithyroidin is beneficial in the psychoses of Graves' disease, which is again shown in the recent reports of Pilez, Becker and Kopystinski. The last-named author, after a relatively short administration, obtained an improvement of the psychical condition, inhibition of the loss of weight, diminution of the goitre and of the remaining symptoms of Graves' disease.

### **Meningococcus Serum.**

Schepelmann reports a case of epidemic cerebro-spinal meningitis, in which the antipyretic and antineuralgic treatment adopted at first had been ineffectual and repeated injections of morphine alone served to alleviate the unbearable headache. Nor did two lumbar punctures have any notable influence on the course of the disease, which first took a decided turn for the better when on the 13<sup>th</sup> day of the disease 35 c.c. of Jochmann's meningococcus serum were administered by intralumbar injection. One further rise of temperature occurred, lasting half a day and accompanied by severe headache, and then the temperature fell within 24 hours by crisis and accompanied by perspiration to 36.9° C., and afterwards re-

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Römheld, Medizinische Klinik 1910, No. 49.

Konried, Medizinische Klinik 1911, No. 26.

Pilez, Medizinische Klinik 1911, No. 5.

Becker, Fortschritte der Medizin 1911, No. 5.

Kopystinski, Oboshrenie Psychiatria 1911, No. 1.

Schepelmann, Wiener klinische Wochenschrift 1911, p. 118.

mained under 37° C. The only secondary effect of the serum noticed by the author was albuminuria lasting for several hours on the day following the injection, and a harmless serum rash in the form of itching urticaria, which was accompanied on the first day by cardiac weakness easily controlled by means of digitalis and camphor. On the 15<sup>th</sup> day after the injection, the patient was discharged cured and free from symptoms. But no marked symptoms of disease were present even 24 hours after the injection. The last symptom to disappear was Kernig's sign, which remained for 11 days after the injection. The case which has been described shows that the serum may be of great benefit even when it has not been administered on the first appearance of symptoms; thus a trial with serum therapy may be advised even if for any reason it has not been employed in the beginning of the disease. But as, according to the communications\*) at hand, the specific treatment of cerebro-spinal fever may claim some degree of confidence, it is better to use the serum as early as possible in every case. Jochmann has recently again emphasised the fact that success depends upon the employment at the earliest possible moment of intralumbar doses, which should not be too small. Special attention may be drawn to this publication of Jochmann, as in it the author discusses fully the method of action, estimation of the value, employment and indications.

Further experiences of serum therapy have been published by C. Mercurios. According to him, the most effective sera were those of Dopter-Pasteur and of Merck. The latter was efficient even in severe cases. A single intralumbar injection of meningococcus serum Merck brought about the cure of a 3-year-old child within 12 hours. In one case, which ran a protracted course in spite of repeated injections of serum, the temperature certainly only fell after injections of iodipin.

### **Polyvalent Bacterial Vaccines.**

In order to promote the more general use of the bacterial preparations necessary for Wright's vaccine treatment, I have for the present undertaken the preparation of the following vaccines:

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\*) Compare Merck's Reports 1906—1910.

Jochmann, Deutsche medizinische Wochenschrift 1911, p. 1733.  
Mercurios, Grèce médicale 1911, No. 15—16.

Gonococcus vaccine	Staphylococcus vaccine
Coli vaccine	Streptococcus vaccine
Pneumococcus vaccine	Typhoid vaccine
Dysentery vaccine	Malta fever vaccine
Tubercle bacilli emulsion.	

The preparation of vaccines is carried out in my serum department; numerous strains of bacteria obtained from different sources are mixed, placed in normal saline solution, to which 0.5 p.c. of phenol is added; if necessary they are heated to 60° or 70° C. until all bacteria are killed. The vaccines are standardised to a content of 400 million bacilli per c. c.; this suspension is called No. I; No. II is also prepared containing 40 million germs in 1 c.c. The vaccines are issued in bottles of 5 c.c. capacity and will keep for months. Bottles which have been opened will also keep for weeks, provided that bacteria have not been allowed to enter; the contents should therefore only be removed by means of a well boiled syringe, and it is also well to clean the groove between the stopper and glass by means of corrosive sublimate solution before opening the bottle.

By "vaccine treatment" is meant the active immunisation of the already infected organism with dead bacteria (vaccines). It has been observed that the introduction of increasing amounts of these organisms causes the more rapid production of protective substances than occurs at the seat of the disease itself. Vaccine treatment is then carried out on the same principle as the prophylactic vaccination for plague, cholera, typhoid fever, etc., and on the basis of the observations which have been made in the immunisation of animals for the purpose of producing antibodies. In the treatment of tuberculosis, this method of "vaccine treatment" introduced by Wright only differs from Koch's treatment by means of emulsions of bacilli, in that Wright did not estimate the result of the separate doses simply by the clinical symptoms like Koch, but made the dose and time of the separate injections depend upon the amount of antibody (opsonin) demonstrable in the patient's blood and estimated after every injection. This estimation of the "opsonic index" has, however, been abandoned in practice as being non-essential and too complicated; and now the same rules are followed in vaccine treatment, which has also been introduced by Wright for various other infective

diseases, as in experimental immunisation, i. e., the most careful clinical observations are made of the reactions occurring after an injection and of the clinical condition of the patient.

These reactions may consist of disturbances of the subjective state of health, of a rise in temperature, of pains and swellings at the site of the injection, more rarely of similar appearances at the diseased part or of an increase in the secretion of diseased mucous membranes.

With regard to the treatment, it may be noted that the statements of different authors still vary considerably. If the following careful scheme be followed, no unpleasant reactions will be experienced.

**Dosage:** Begin with 0.1 c. c. of No. II (4 millions) and double the dose at each consecutive injection until 1 c. c. of No. I is reached; this dose may be continued for some time in chronic disease. Should a reaction occur, the last dose is repeated without being increased. The intervals between the injections may at first be short — 2 to 4 days — with small doses and so long as there is no reaction. Should any reaction occur, the interval is prolonged, to at least 8 to 10 days until the local pains disappear. When a dose of 1 c. c. of No. I has been reached, an injection is only given every 8 to 14 days, and this treatment may be continued for months.

The site of the injection may be chosen at will (upper arm, thigh, abdominal wall or lumbar region). The injection must be carried out with the most careful antiseptic precautions.

#### Indications:

Staphylococcus vaccine in furunculosis, acne, eczema, suppuration of the middle-ear, suppuration of the accessory sinuses of the nose, pyorrhœa alveolaris, mastitis.

Streptococcus vaccine in cellulitis, abscesses, mixed infection in phthisis, articular rheumatism, erysipelas.

Typhoid vaccine in typhoid fever and dysentery.

Coli vaccine in cystitis, pyelitis, appendicitis.

Gonococcus vaccine in gonorrhœa, and especially in chronic diseases of the joints, in epididymitis and prostatitis.

Pneumococcus vaccine in pneumonia, appendicitis, ulcer serpens corneæ, bronchitis.

Malta fever vaccine in Malta fever.

Tubercle bacilli emulsion in all stages of tuberculosis, or in conjunction with tuberculous treatment.

For the above named diseases I always keep a stock of vaccines. Further, it should be noted that for some cases, especially of coli diseases, the employment of "auto-vaccines" has been suggested, i. e., of vaccines prepared from a culture of bacteria taken from the patient himself. If an auto-vaccine is desired, it is prepared in my serum department on receipt of a pure culture or of suitable material taken from the patient.

#### Literature on Treatment with Vaccines:

- Wright, British Medical Journal 1900, I, p. 122, II, p. 112, 1901, I, p. 336, 642, 647, 1072, II, p. 1226.
- Rufenacht, Internationales Zentralblatt für die Tuberkuloseforschung 1911, No. 7.
- Noeggerath, Therapeutische Monatshefte 1911, No. 8.
- Wolffsohn, Berliner klinische Wochenschrift 1908, No. 49 and 1909, No. 22.
- Dmitrenko, Russkij Wratsch 1911, No. 9. (Pneumonia.)
- Selley, Medizinische Klinik 1911, p. 1383. (Gonorrhœal Prostatitis and Arthritis.)
- Menzer, Münchener medizinische Wochenschrift 1911, p. 2434. (Gonorrhœa.)
- Bruck, Münchener medizinische Wochenschrift 1911, p. 2616. (Gonorrhœa.)
- Schultz, Deutsche medizinische Wochenschrift 1911, p. 2331. (Gonorrhœa.)
- Rygier, Deutsche medizinische Wochenschrift 1911, p. 2334. (Vulvovaginitis.)
- Hecht-Klausner, Berliner klinische Wochenschrift 1911, p. 894. (Gonorrhœa.)
- Schmitt, Münchener medizinische Wochenschrift 1911, p. 1846. (Gonorrhœa.)
- Jacowleff-Jassnitzki, Russkij shurnal kosnych i veneritscheskich bolesnej 1911, June. (Gonorrhœa.)
- Voss, Münchener medizinische Wochenschrift 1911, p. 2245. Staphylococcal infection of the external auditory canal.)
- Russel, Bulletin of the Johns Hopkins Hospital 1910, March. (Typhoid.)
- Stone, Journal of the American Medical Association 1910, Vol. 55, p. 1708. (Typhoid.)
- Bruck, Deutsche medizinische Wochenschrift 1909, p. 470. Medizinische Klinik 1910, p. 811. (Gonorrhœa.)
- Schindler, Berliner klinische Wochenschrift 1910, p. 1446. (Gonorrhœa.)
- Jarvis, Presse médicale 1910, p. 161. (Gonorrhœa.)
- Sowinsky, Russkij Wratsch 1910, p. 700. (Gonorrhœa.)
- Merkurief, Russkij Wratsch 1911, p. 193. (Gonorrhœa.)
- Craig, Medical Record 1911, 18<sup>th</sup> November. (Streptococcal and Staphylococcal infections.)

- Merkuriet-Silber, Wiener klinisch-therapeutische Wochenschrift 1911, No. 28. (Gonorrhœa.)
- Reiter, Deutsche medizinische Wochenschrift 1910, p. 1933. — Berliner klinische Wochenschrift 1911, No. 27. (Gonorrhœa.)
- Friedländer-Reiter, Berliner klinische Wochenschrift 1910, p. 1663. (Gonorrhœa.)
- Boellke, Deutsche medizinische Wochenschrift 1907, p. 1487. (Acute infectious diseases.)
- Kelly, British Medical Journal 1908, II, p. 1150.
- Strubell, Deutsche medizinische Wochenschrift 1910, p. 838. (Diseases due to staphylococci.)
- Wolff and Reiter, Deutsche medizinische Wochenschrift 1909, p. 1177. (Tuberculosis.)
- Munk, Medizinische Klinik 1911, p. 1668.
- Compare also Merck's Reports 1909, p. 77 and 1910, p. 337.

### Pyocyaneus-Protein Honl.

Pyocyaneus-protein was formerly recommended for the treatment of ulcers of the leg, as Honl and Bukovsky, and also Jesensky, had obtained surprising results by the use of this bacterial preparation in the condition in question\*). According to a new report by J. Lang, the preparation also deserves the consideration of the physician in the treatment of tonsillitis and pharyngitis. The author acted on the assumption that the preparation exerted an antagonistic action on various microbes, especially those causing suppuration, and he prescribed it in 65 cases of mild and severe tonsillitis, even in those in which cellulitic infiltrations had already formed in the neighbourhood of the tonsils. The medicament was applied to the inflamed part in sufficient amount on a plug of cotton wool once daily. The results were as follows: Of 20 mild cases of tonsillitis, 9 were cured in 1 day, 11 in 2 days. Of 23 severe cases of tonsillitis, 12 were cured in 2 days, and 7 in 3 days. In 4 cases, in spite of treatment, cellulitis occurred around the tonsils, but was not very extensive. One of these cases of cellulitis was cured in the course of 4 days by further treatment with pyocyaneus-protein, 2 opened of their own accord and one had to be incised. In the last 3 cases 5 to 6 days were required for the cure. Of 22

Honl-Bukovsky, Abhandlungen der böhmischen Akademie der Wissenschaften 1898, Jahrgang VII. — Wiener klinische Rundschau 1900, No. 5.

Jesensky, Dental Cosmos 1901, July.

\*) Compare Merck's Report 1901, p. 151.

Lang, Casopis lekaruv ceskych 1911, No. 3.

cases of mild cellulitic infiltration, by treatment with pyocyaneus-protein 1 was cured in 1 day, 9 in 2 days, 5 in 3 days, 5 in 4 days, and one severe case in 6 days. In only one case did cellulitis occur and required incision. Thus the results were very satisfactory. The author also points out that the preparation was very well tolerated by the patients.

### **Syphilis Diagnostic according to von Dungern.**

The utility of von Dungern's diagnostic for syphilis finds confirmation in the communications\*) of A. Knick, E. Wehrli, J. Zilz, Lang, J. Schereschewsky, A. Steyerthal, O. Roth, G. Gali, A. Guisan and Taussig, whereas it is doubted by J. Kahn and O. Stiner. The failures of the last-named authors may probably be explained by the recent discovery that the reliability of the diagnostic ceases when it is kept for a long time. In order that those wishing to use the diagnostic may always obtain freshly prepared reagents, I have decided only to send the preparation directly to those making use of the same. If the reagents required for the Dungern test are always used fresh, viz., not older than at most a week, no more failures will be recorded. Should several days be required in transit, as in the case in sending it to long distances, the investigator must prepare his own complement, for which purpose he may adopt the following method of preparation.

A guinea-pig weighing at least 250 grammes is obtained, the hairs are carefully shaved from the neck and the part washed with normal saline solution (not water). An assistant then holds the animal with its abdomen downwards; both

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\*) Compare Merck's Report 1910.

Knick, Monatsschrift für Ohrenheilkunde 1911, Vol. 45, No. 7.

Wehrli, Schweizer Rundschau für Medizin 1911, No. 12.

Zilz, Ashs Wiener Vierteljahres-Fachblatt für Stomatologie 1911, No. 2.

Lang, Schweizer Wochenschrift für Chemie und Pharmazie 1910, No. 53.

Schereschewsky, Deutsche medizinische Wochenschrift 1911, No. 18.

Steyerthal, Fortschritte der Medizin 1911, No. 6.

Roth, Korrespondenzblatt für Schweizer Ärzte 1911, No. 8.

Gali, Budapesti Orvosi Ujsag 1911, No. 11.

Guisan, Schweizer Rundschau für Medizin 1911, No. 47.

Taussig, Casopis likaruv českých 1911, No. 44.

Kahn, Berliner klinische Wochenschrift 1911, No. 16.

Stiner, Korrespondenzblatt für Schweizer Ärzte 1911, No. 33.

carotids are then cut through by means of a rapid incision and the blood (about 8 c. c.) is collected in a beaker. From this point the treatment varies, according as to whether the physician possesses a centrifuge or not.

If the physician possesses a centrifuge, the blood is first poured into an ordinary medicine bottle, the bottom of which is covered with glass beads, and shaken for 10 minutes. The defibrinated blood is centrifugalised, by which means the serum (complement) separates to form an upper layer.

If the physician does not possess a centrifuge, the blood is allowed to stand in the medicine bottle for 6 to 8 hours at the temperature of the room, when a few c. c. of serum will have separated.

From this it is seen that the physician who does not possess a centrifuge should prepare the complement in the evening, and carry out the test on the following morning; on the third day this complement has usually lost its efficacy.

As the action of the complement of fresh guinea-pig's serum is not always entirely uniform, the course of the control test must be watched before applying the test. The control test is first carried out with 0.05 c. c. of complement when hæmolysis will generally be seen to ensue. Should no solution occur, the complement must be exceptionally weak and a second control test is made, using 0.075 c. c. of complement. Should this also fail, 0.1 c. c. must be used for the next test. (Should this amount also prove ineffective, the guinea-pig's serum is useless for some reason, but this very rarely happens.) The real test is then undertaken, using the amount of complement which gave a definite action in the control test.

A. Knick illustrates the value of the syphilis test of von Dungern on the basis of his own experiments in the field of oto-rhino-laryngology. According to him, it was of excellent service in doubtful cases of lues, as it gave many a valuable hint regarding diagnosis and treatment and assisted in preventing many a faulty diagnosis, experimental excision or operation. A positive result always gave considerable support to the diagnosis and was usually confirmed by the treatment. The author emphasises as a feature of special assistance that the physician is no longer dependent upon the anamnesis, which is often so deceptive and defective. But in order to avoid false conclusions, it

must be remembered that a positive reaction only gives a general indication of the presence of syphilitic infection and does not prove the affection in question to be syphilitic in nature; further that a negative reaction does not absolutely exclude the possibility of syphilitic infection, as primary affections usually give a negative reaction at first, even with the Wassermann method. In primary affections of the tonsils, which may be very similar in appearance to Plaut-Vincent's angina, the serum test fails as a diagnostic for syphilis, and in these cases only the discovery of spirochetes is decisive. If, therefore, there is a grave suspicion of lues and Dungern's test fails, the Wassermann reaction may be tried or the more sensitive tests of Hecht and Stern. Otherwise the Dungern test is as serviceable as the Wassermann reaction, and is at the same time easy to carry out and to learn, and requires less time than the Wassermann method. It is therefore specially suitable for every-day practice, and particularly for specialists and for laboratories not fitted up for carrying out complicated tests. According to Knick, it should prove particularly useful in the special branch of otorhino-laryngology, as the diagnosis of syphilis is often very difficult in these cases. But in other special branches of medicine, Dungern's modification of the Wassermann test is also a valuable aid in the diagnosis of possible syphilis; thus it is recommended by E. Wehrli in initial tabes and paralysis, and for rapid diagnosis in keratitis parenchymatosa, iritis, etc., and by J. Zilz for the diagnosis of syphilitic processes in the buccal cavity.

### Silver, Colloid

Further communications as to the value of collargol and similar preparations of silver in septic processes have been published by Trembur, K. Vogel, Decker, J. Hirsch and Boshardt. Trembur gave 5 intravenous injections at intervals of 5, 10, 5 and 15 days, each injection consisting of 5 c.c. (85 min.) of a 2 p.c. collargol solution, to a patient aged 7, suffering from severe mycotic endocarditis, pericarditis

Trembur, *Münchener medizinische Wochenschrift* 1911, p. 599.

Vogel, *Medizinische Klinik* 1911, p. 1267.

Decker, *Dissertation Bonn* 1910.

Hirsch, *Medizinische Klinik* 1911, p. 1084.

Boshardt, *Korrespondenzblatt für Schweizer Ärzte* 1911, No. 23.

and myocarditis; he was completely successful. All symptoms disappeared, except the mitral insufficiency, the general condition improved and the fever abated. In other cases collargol also rendered good service. Each injection was followed by leucopenia, and later by leucocytosis, which was in some cases considerable; the ferments set at liberty by the breaking down of the leucocytes cause the intoxication of the organism, which is accompanied by a rise of temperature to  $40^{\circ}\text{C}$ ., or higher. Vogel also expresses himself satisfied with the action of collargol, when injected intravenously, in severe septic wounds and in sepsis following parametritic abscesses, tumours of the spinal cord and burns. He thinks less highly of the rectal method of administering the drug, for in about 20 cases which had not been benefited by the rectal application, he obtained good results by its intravenous injection. Decker, on the other hand, found rectal injections very beneficial in a series of gynæcological cases. They always had a good effect on the fever, but the injections had to be repeated several times in order to obtain lasting benefit. According to Decker, collargol enemata always act more effectively than the application of the ointment, they are, in the author's experience, similar in action to intravenous injections and are besides simpler to administer and less dangerous. Decker suggests 0.5 to 2 grammes ( $7\frac{1}{2}$ —30 grains) as a dose. Hirsch gave 5 to 6 grammes (75—90 grains) daily per rectum, in the form of 2 to 3 enemata of 100 grammes ( $3\frac{1}{3}$  oz) of a 2 p.c. solution. Boshardt also recommends the use of large doses, 2 to 3 grammes (30 to 45 grains), to be given rectally. When the action commences the dose may be reduced. F. Krämer prescribed in erysipelas doses of 1 to 1.25 grammes (15—20 grains) of collargol per rectum with good results.

In septic conditions following gonorrhœa, treatment with inunctions of silver, according to Gennerich, gives useful results. For this purpose 3 to 5 grammes (45—75 grains) of unguentum Credé are gently rubbed in with the hand once or twice a day; this may be continued for weeks. This treatment is, however, not very satisfactory, for the action takes place slowly and is not sufficiently pronounced. Intravenous

injections of collargol act better, but are not suited for continuous use on account of the severe constitutional reaction they cause and the prostration which follows. Neither are collargol enemata suitable for this method. Subcutaneous injections of electrargol are said to answer better, as this preparation is well borne for prolonged periods and in large doses. The usual dose is 10 c.c., but 20 or 30 c.c. may be injected. This drug has a rapid and certain antipyretic action, and local symptoms of inflammation, swellings and pain disappear under its influence.

In rhinology, colloid silver has proved an effective and non-irritant antiseptic; it has the one disadvantage that it stains the skin. H. Bourgeois used it especially for children in protracted cases of acute rhinitis with purulent discharge and in chronic purulent rhinitis, in the form of drops, ointment and paint. For instillations for young children, electrargol is best used in isotonic solution; the child is laid on its back and 4 drops are instilled into the nostril. This application may be repeated 4 times in the course of the day. For older children an ointment may be prescribed, consisting of 2 grammes (30 grains) of collargol, 2 grammes (30 min.) of liquid paraffin, 10 grammes ( $\frac{1}{3}$  oz) of lanolin and 10 grammes ( $\frac{1}{3}$  oz) of vaseline; the mucus must be removed before applying the ointment. For adults the mucous membrane is first anaesthetised with a solution of cocaine (1:30), and then painted with a 5 to 10 p.c. solution of collargol.

G. Barbézieux and Picard report on the favourable results of collargol treatment in cholera. They used a collargol solution of 1:100, and gave a subcutaneous or intravenous injection of 2 to 6 c.c. daily. They also prescribed the use of opium, alcohol, lactic acid and intestinal antiseptics as well as the collargol. As a consequence of the collargol injections the spasms soon ceased and the general strength improved; the diarrhoea was also kept in check, but the vomiting was only slightly improved. The chief advantage of treatment with collargol lies in its action and simple application.

Bourgeois, Progrès médical 1911, No. 3.

Barbézieux-Picard, Presse médicale 1910, p. 760. — Bulletin de la Société médico-chirurgicale de l'Indo-Chine 1910, p. 362.

### Silver and Potassium Cyanide.

Silver and potassium cyanide,  $\text{AgKCy}_2$ , forms colourless crystals, readily soluble in water and should be kept in brown tinted glass bottles on account of its sensitiveness to light. As I have already reported\*), the aqueous solution of this double salt has powerful bactericidal properties, so that one part added to 50,000 parts of blood serum checks the growth of anthrax bacilli. In spite of this fact, established by Behring, the preparation has not been used therapeutically. A. Philipppson has recently recommended it for the treatment of chronic gonorrhœa. As regards the toxic properties of the preparation, H. C. Plaut has found that rabbits can stand intravenous doses of 0.0015 to 0.006 gramme without harm. On the other hand, a dose of 0.01 gramme given to a rabbit weighing 2620 grammes caused convulsions, followed by disappearance of the reflexes, opisthotonos and maximal dilatation of the pupils. After half a day the animal had recovered. As a result of this experiment, the author concludes that a dose of 0.27 gramme (4 grains) might endanger the life of an adult man. According to this, it would be about as poisonous as potassium cyanide.

After having made careful tests with well diluted solutions, the author has for several years used silver and potassium cyanide solely for washing out the urethra and bladder in the concentration of 0.032 to 0.67 in 200 of water, which is equivalent to a mixture of 4 to 80 drops of a solution of 6 grammes of silver and potassium cyanide in 30 grammes of water with 200 grammes of water. With this he has never even had a suspicion of toxæmia. As a further precaution he does not use it when hypertrophy of the prostate is present or in other conditions in which retention of urine might occur, nor does he allow the patient to handle the preparation.

The action of silver and potassium cyanide is, in Philipppson's opinion, not inferior to that of silver nitrate. The turbidity of the urine, the shreds and flakes in the urine, the morning discharge, all gradually disappear as a result of the lavage. Cases with few gonococci, which have passed

\*) Merck's Bericht 1890, p. 18.

Behring, Zeitschrift für Hygiene 1889, p. 467.

Philipppson, Münchener medizinische Wochenschrift 1911, p. 468.

Plaut, communicated by Philipppson.

the early stage of irritation, are cured by the use of dilute solutions, in the same way as are cases treated with dilute solutions of silver nitrate. But if these conditions are absent, or if stronger solutions are used than the clinical condition justifies, the disease is made worse as is the case with all antigonorrhœic remedies. The author considers that silver and potassium cyanide has the following advantages over silver nitrate: that warmed tap-water may be used for its solution, as no turbidity ensues; that it is better borne, because cyanide compounds probably have an anæsthetising action; and that it does not stain.

For recent gonorrhœa Philippson has also tried lavage; he used a mixture of one drop of the concentrated silver and potassium cyanide solution mentioned above (6 + 30) with 200 grammes of water. The palliative effect was most satisfactory, but the final cure was not brought about any more rapidly than by the use of the gonorrhœal syringe and of ichthargan.

### Silver Nitrate.

For the local treatment of ulcers of the leg Althoff gives the following instructions: After cleansing the sore with soap and water, washing with corrosive sublimate solution, and after treating it for several days with compresses of aluminium acetate solution, the sore is dressed twice a day by the patient himself. Every time the bandage is changed the whole leg below the knee is bathed for 5 minutes in lukewarm water. At night the sore is covered with a moist corrosive sublimate compress (1:1000) reaching not more than 1 to 2 cm. ( $\frac{2}{5}$ — $\frac{4}{5}$  in.) beyond the edge of the ulcer and covered over with some waterproof material. In the daytime a fairly thick layer of the following ointment is applied to the ulcer:

Rp. Argent. nitr.	0.75 gramme (12 grains)
Balsam. Peruv.	2.50 grammes (40 grains)
Vaselin. alb.	ad 50.00 grammes ( $1\frac{2}{3}$ oz)

These alternate dressings of silver nitrate and corrosive sublimate in most cases brought about a surprisingly rapid cure of the ulcer.

Engel and Turnau have suggested the following method for distinguishing between the urine of breast-fed and bottle-fed children: To about 5 c.c. of the urine to be tested 15 to 20 drops (1 c.c.) of a 2 p.c. solution of silver nitrate are added, without previous acidification. The mixture is left for about 10 minutes. If the precipitate turns rapidly black, the urine is certainly that of a breast-fed child. If a still more rapid method is required, the mixture of urine and silver nitrate should be boiled. If the precipitate remains white or is only slightly coloured, the urine is certainly not that of a breast-fed child. If a fairly intense coloration results the procedure should be repeated at the temperature of the room in order to obtain a decisive result. As F. Boschan doubted the value of this test, Engel and Turnau, in a later communication, stated that the result of the reaction was only of diagnostic value provided the instructions were exactly followed, viz., if sufficient silver nitrate were added. If less silver nitrate is used than is necessary to combine with the total chlorides of the urine, even the urine of a breast-fed child will not darken; if the prescribed amount be used, the urines of breast-fed children will react, but not those of children fed with cow's milk, because they usually contain more chlorine, and the amount of silver used will not suffice to combine with all the chlorine present. If the amount of silver nitrate added is increased above the point of saturation in the urines of children fed on cow's milk, discoloration will take place, but it will be clay-coloured or reddish-brown. A test described by G. Tugendreich by which human milk can be distinguished from cow's milk, is also apparently worked out on a similar basis. If 3 c.c. of human milk be added to 8 c.c. of a 1 to 2 p.c. solution of silver nitrate, and the mixture quickly heated to boiling point, and allowed to boil 3 times, the mixture assumes a colour ranging from that of café au lait to brownish violet. Cow's milk either does not give this reaction at all, or only to a slight degree.

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Engel-Turnau, *Berliner klinische Wochenschrift* 1911, p. 18.

Boschan, *Berliner klinische Wochenschrift* 1911, p. 302.

Engel-Turnau, *Berliner klinische Wochenschrift* 1911, p. 303.

Tugendreich, *Berliner klinische Wochenschrift* 1911, p. 224.

### Silver Proteinate.

Silver proteinate (Heyden) is a brownish-yellow powder, readily soluble in water, insoluble in alcohol and ether. According to M. Oppenheim, the same amount of care is necessary in the preparation of aqueous solutions as with similar silver preparations, for the author states that it must be carefully poured on to cold water and allowed to dissolve. It fulfils all the requirements of an antigonorrhœic, for it possesses the property of killing gonococci and has a certain deep action on the tissues, and does not cause precipitation in the presence of sodium chloride or of albuminous substances. Oppenheim found that it contained 8.21 p.c. of silver.

The author has tested silver proteinate in over 300 cases of gonorrhœa. As a result of these experiments he considers it to be an antiseptic with only a slight astringent or irritant action, for which reason it is suitable for abortive treatment in quite recent cases, and for the early treatment of urethritis acuta anterior and posterior, at a time when the destruction of the gonococci is of importance.

In the abortive treatment the urethra was washed out daily by means of a Majocchi nozzle. A 0.25 p.c. solution of silver proteinate was used to begin with, and gradually increased to 0.75 p.c. At the same time the patients were advised to instil a 0.15 p.c. solution into the urethra for 5 minutes every morning and evening. After the treatment had been continued for 10 to 14 days, injections of silver nitrate solution were prescribed, at first a 0.5 p.c. solution being used, gradually increasing the strength to 2 p.c. Oppenheim considers the results obtained (about 50 p.c. of cures) to be very favourable, as they are not worse than the results of treatment with similar preparations of silver. It should be noted that he prefers to use dilute solutions, as described, for abortive cures, as they give better results than concentrated solutions (5—7.5 p.c.).

For the treatment of a first attack of urethritis anterior the author prescribed 3 injections of silver proteinate solution daily. At first a solution of 0.3:200 was used, this was increased in 5 days to 0.6:200, and in 8 days to 0.8:200. The last part of the treatment consisted in injections of an antiseptic, astringent preparation of silver, e. g., ichthargan

(0.5 to 0.2:200), albargin (0.1 to 0.25:200), or silver nitrate (0.25 to 2:100) into the urethra.

In urethritis posterior acuta the method of treatment was the same as for urethritis anterior, but besides the injections, 1 gramme (15 grains) of sodium salicylate was given internally 4 times a day. Oppenheim warns against using concentrated silver solutions in the treatment of urethritis posterior. On the other hand, when silver proteinate was injected in a concentrated form (1 to 2:200) at the commencement of a case of urethritis anterior subacuta, which had occurred either as a result of repeated infections or was due to infection some time back, it showed a corresponding action on the gonococci and consequently a diminution in the secretion, but no direct influence on the latter. Hence the preparation cannot be used as a means of limiting the secretion.

### Sodium Bicarbonate.

In the treatment of the acid intoxication of diabetic coma, the internal administration of even large doses of sodium bicarbonate does not always prove sufficient. The intravenous application of the drug offers more prospect of success, and gives good results, as is evident from the communications of R. Lépine, Sicard, M. Labbé and P. Carrié. Thus Labbé and Carrié report a case in which on several consecutive days they administered 500 c. c. (17 oz) of a 3 p. c. sodium bicarbonate solution by intravenous injection, besides giving 20 grammes ( $\frac{2}{3}$  oz) of the salt internally. By means of this treatment the somnolence disappeared, the acidity of the urine became normal and the excretion of ammonia was diminished. The acetoneuria alone diminished more slowly. The case was cured. Sicard recommends the employment of the injections not only in the actual comatose stage, but also in the premonitory stage and in other symptoms of diabetes, such as pruritus and pains. He states that a rapid action is obtained without affecting the blood pressure by the infusion of 100 to 250 c. c. ( $3\frac{1}{3}$ — $8\frac{1}{3}$  oz) of a 10 p. c. solution, which may be repeated at intervals of a few days. Lépine also prescribes the injections

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Lépine, Progrès médical 1911, No. 18.

Sicard, Revue de thérapeutique 1911, p. 488. — Presse médicale 1911, p. 519.

Labbé-Carrié, Revue internationale de médecine 1911, p. 250.

in diabetes, if other measures have failed. But he only uses a 1·7 p.c. solution. He expects less good results in actual coma than in acetonæmia in the pre-comatose stage, as coma may supervene at any time during the course of acetonæmia. The author gives as a maximum dose 2 litres (66 oz) of an isotonic, 1·7 p.c. sodium bicarbonate solution, i. e., 34 grammes (510 grains) of sodium bicarbonate.

E. Binet has studied the question as to whether sodium bicarbonate is harmful in the treatment of gastric affections. He came to the conclusion that given in single doses of 0·75 to 1 gramme (12—15 grains), and in daily doses of 5 grammes (75 grains), it is quite harmless and has a favourable effect on the motility, the sensibility and the secretory function of the stomach. The author considers that larger doses are quite unnecessary in the treatment of hyperchlorhydria.

Attention may be drawn to the suggestion by E. Fuld of making use of sodium bicarbonate as a direct test for free acids in the stomach. It is carried out by giving the patient a draught of sodium bicarbonate solution after a test meal. On auscultation a crackling sound is heard if free acid be present in the stomach; it is due to the bursting of carbon dioxide bubbles. The method was formerly recommended by A. L. Benedict.

### Sodium Choleinate.

While the employment of bile and its preparations in constipation is universally recognised as a useful form of treatment\*), new suggestions as to its administration are constantly met with in the literature. Thus Singer and Glässner last year recommended the administration of bile in hardened gelatin capsules, but as a rule, prefer its rectal employment in the form of suppositories. Inouye and Sato be-

Binet, Progrès médical 1911, No. 3. — Wiener klinische Wochenschrift 1911, No. 13.

Fuld, Berliner klinische Wochenschrift 1910, p. 2009 and 1911, p. 717.

Benedict, New York Medical Journal 1911, p. 466.

\*) Compare Merck's Report 1908.

Singer-Glässner, Merck's Report 1910, p. 345.

Inouye-Sato, Boas Archiv für Verdauungskrankheiten 1911, Vol. 17, No. 2.

lieve that bile should be given in a large amount of water, as by this method the digestion of albumin is not interfered with. For this purpose purified ox bile in doses of 0.5 to 1.0 gramme ( $7\frac{1}{2}$ —15 grains), or sodium choleinate in doses of 0.3 to 0.6 gramme (5—10 grains) may be used and are best given an hour before meals. To mask the taste, sugar and peppermint water are prescribed. Sodium choleinate may also be prescribed in the form of pills. Although bile has a very unpleasant, bitter taste, the two authors have never met with an uncontrollable aversion to the drug. Besides its action in promoting the absorption of fat, bile is well known to possess an aperient action, for which reason the simultaneous use of laxatives should be avoided. As is evident from a large number of cases communicated by the authors, bile is an effective drug in the treatment of the symptoms of icterus due to deficient secretion of bile.

### Sodium Citrate.

Sodium bicarbonate, which is much used in the treatment of acidosis, has the disadvantage that the carbon dioxide it liberates causes gastric discomfort. In addition, large doses occasionally lead to vomiting and diarrhoea. As acidosis depends upon the fact that strong acids, when excreted, withdraw considerable amounts of alkali from the organism and thus lead to deficiency of alkali, the suggestion has been made to administer the salts of those acids which on oxidation in the organism liberate carbon dioxide and thus supply the necessary alkalis. For this purpose L. Lichtwitz recommends the use of sodium citrate. It has a slightly salty, but not unpleasant taste and may be given either by itself dissolved in water, or with food. It does not incommode the stomach or intestines and thus causes neither loss of appetite nor diarrhoea, even if daily doses of 50 grammes ( $1\frac{2}{3}$  oz) be taken. As the oxidation of citric acid takes place even in severe diabetes, sodium citrate can also be given with benefit in these cases. After the administration of a daily dose of 30 grammes (1 oz), the  $\text{NH}_3$ -excretion was decreased in a case of diabetes mellitus of medium severity. On discontinuing the treatment, it returned to the original amount. Besides, in diabetes the antiketogenetic

action of sodium citrate, noted by Satta, Baer and Blum, comes into play. Possibly sodium citrate will be found of service in the infusion treatment of diabetic coma in place of sodium bicarbonate. The author intends to carry out experiments in this direction.

Variot has recently again drawn attention to the value of sodium citrate in the vomiting of young babies. According to him, babies can take 2 grammes (30 grains) a day in milk without fear of ill effects. The best solution to use is made up of 2.5 grammes (38 grains) of sodium citrate in 125 grammes (4 oz) of water and 25 grammes ( $\frac{3}{8}$  oz) of syrup; of this a tablespoonful is given to a breast-fed child before every meal, or an equal quantity is added to the milk. The action of the drug is practically always immediate, like the action which follows the administration of an antispasmodic. If necessary, 6 to 7 tablespoonfuls of the solution may be unhesitatingly given during the day, for the failure of this form of treatment is usually due to too small dosage.

### Sodium Fluoride and Zinc Fluoride.

The employment of fluorides for the preservation of building wood has recently been strongly recommended by R. Nowotny, for according to Malenkowic and Netzsch, the fluorides, which can now be prepared technically in suitable, inexpensive qualities, are far superior in their preserving power to copper sulphate and zinc chloride, which have hitherto been employed for the preservation of wood. The procedure suggested by Malenkowic, based on the employment of sodium fluoride and zinc fluoride, is said to give specially good results, for it is converted in the wood to  $\text{ZnF}_2(\text{ZnF})_2\text{O}$ , a compound soluble with difficulty and possessing considerable

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Satta, Beiträge zur chemischen Physiologie und Pathologie (Hofmeister) 1905, p. 376.

Baer-Blum, Beiträge zur chemischen Physiologie und Pathologie 1907, p. 11.

Variot, Revue de thérapeutique 1910, p. 757. — Compare Merck's Report 1905, p. 140.

Nowotny, Chemiker-Zeitung 1911, p. 546. — Österreichische Chemiker-Zeitung 1910, No. 7.

Malenkowic, Die Holzkonservierung im Hochbau, Wien, Leipzig 1907.

Netzsch, Die Bedeutung der Fluorverbindungen für die Holzkonservierung. Dissertation München 1909.

antiseptic power. The impregnation of wood with both these salts is therefore specially suitable for the preservation of wooden masts and telegraph poles which are exposed to all weathers; whereas for building woods, which are as a rule protected from the weather, impregnation with sodium fluoride generally offers sufficient protection from the destructive dry-rot. The inhabitants of the houses need fear no harm to their health from the impregnation of the building wood with fluorides.

### Sodium Glycocholate.

The Porges syphilis test\*), according to the investigations of O. Herman and A. Perutz, has proved to be specific, and is apparently only slightly less frequently definite in syphilis than is the Wassermann test. The test is rendered more serviceable by the inclusion of the suspension of colloid cholesterin for this serum diagnosis of syphilis, for by this means the precipitates are more bulky and the test is thus rendered more definite. The test is carried out as follows: The blood is obtained by pricking the ball of the finger and is left to stand for a few hours to allow the serum to separate; after removing the blood corpuscles (by centrifugalising), it is inactivated by heating to exactly 55° C. for half an hour. The serum must not be strongly hæmolytic. From a stock solution consisting of 2 grammes of sodium glycocholate, 0.4 gramme of cholesterin and 100 grammes of alcohol (95 p. c.) a dilution with distilled water 1:20 is prepared, and also a fresh solution of sodium glycocholate in water 2:100 for each examination. To 0.4 c. c. of the serum mentioned above and introduced into a test-tube about 5 mm. in diameter 0.2 c. c. of the stock solution diluted with twenty times its volume of water and 0.2 c. c. of the 2 p. c. sodium glycocholate solution are added, the test-tube is plugged with cotton wool and well shaken. This mixture is allowed to stand for 20 hours at the ordinary temperature. A definite precipitate alone signifies a positive reaction, while cloudiness and very fine flakes must be left out of account. The result must be read without previous shaking.

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\*) Compare Merck's Report 1910, p. 346.

Herman-Perutz, Medizinische Klinik 1911, p. 60.

A new test for syphilis is described by Loeper, Desbouis and Duroeux. It may be described as a cutaneous test (dermo-reaction or intradermo-reaction), as the positive result is recognised by cutaneous symptoms. The authors started from the fact that syphilitic blood serum is precipitated by sodium glycocholate (Porges' reaction) and they tried whether the subcutaneous injection of this salt would cause any reaction with the blood of syphilitic patients. For this purpose they injected into syphilitic, and non-syphilitic, patients 1 to 2 drops of a freshly prepared 2 or 5 p.c. solution of sodium glycocholate and found that non-syphilitic patients gave no reaction. In primary, secondary and tertiary syphilis, on the other hand, a reaction always occurred, which took the form of lenticular erythema, consisting of painful nodules the size of a millet-seed or lentil, or of a small, slowly cicatrising sore. These symptoms appeared 18 to 36 hours after the injection and lasted for 2 to 5 days. They may be accompanied by febrile symptoms and pain. In parasyphilitic diseases, such as tabes, progressive paralysis and leucoplakia, a reaction is rarely obtained. The results are said to be parallel with those yielded by the Wassermann and Porges tests.

### Sodium Iodate.

Experiments with sodium iodate ( $\text{NaIO}_3$ ) led W. Uftjuschandinoff to the conclusion that this salt is useful in Asiatic cholera if not employed too late. He gave his patients a subcutaneous injection of 1 c.c. (17 min.) of a 7 p.c. aqueous solution every 3 hours, a method which gives rise to no pain or local irritation and only rarely causes iodism. In comparison with other methods of treatment, the author by this means effected a striking decrease in the mortality (26 to 46 p.c.); excluding those cases which were moribund at the commencement of treatment, the mortality amounted to 16 p.c. The author was also able to observe that in the cases which could not be saved the fatal issue was considerably delayed by his method of treatment. From this he concludes that sodium iodate diminishes the virulence of cholera vibrios without killing them, for otherwise the liberation of the endotoxins would cause death to ensue more rapidly

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Loeper, Desbouis, Duroeux, *Progrès médical* 1911, No. 3.

Uftjuschandinoff, *Praktitscheskij Wratsch* 1911, No. 10.

and not more slowly, as was the case following the administration of sodium iodate. Whether the action of the drug is due to the iodine or to the oxygen which it contains, or perhaps to both, cannot be settled with certainty. It may be noted that the author at first injected a 10 p.c. sodium iodate solution and later used a 7 p.c. solution, as the former proved too concentrated. To children he administered a 3 p.c. solution in suitable amounts.

### Sodium Iodide and Hydrogen Peroxide.

A new method of treating local infective processes, which has been received with special interest by dermatologists, has recently been published by S. A. Pfannenstill. It consists in supplying sodium iodide (or potassium iodide) to the infected tissue through the circulation by administering the salt internally, and at the same time, by suitable means, applying hydrogen peroxide (or ozone) externally. By the interaction of the iodine salt and  $H_2O_2$  in the blood iodine is set free, and to its bactericidal power the effectiveness of the method is due. But, according to the author, this is only of value in ulcerative infective local processes. This condition can, if necessary, be induced by operation or even by employment of the method itself.

Pfannenstill's method is indicated in tuberculous laryngitis, in lupus and external tuberculosis, in lupus of the mucous membranes and in non-tuberculous local infections. In tuberculous laryngitis sodium iodide was used internally and ozone inhalations externally, and in the other conditions  $H_2O_2$  in place of ozone.

Pfannenstill's treatment of lupus of the mucous membranes was studied in detail by O. Strandberg, who carefully worked out the procedure. The patients are given 1 to 3 grammes (15—45 grains) of sodium iodide a day, divided into 6 doses, and this is continued for 4 to 5 days, during which period the nasal cavity is freed from scabs in a special

Pfannenstill, *Hygiea* 1910, May—June. — *Nordisk Tidskrift for Terapi* 1911, January. — *Zentralblatt für die gesamte Therapie* 1911, p. 449. — *Deutsche medizinische Wochenschrift* 1911, p. 2420.

Strandberg, *Berliner klinische Wochenschrift* 1911, p. 166 and 1755. — *Dansk Klinik* 1910, No. 48.

way. Then, while continuing the iodine medication, previously boiled gauze tampons free from starch are introduced into the nose twice a day, having been previously moistened with a mixture of 3 p.c. of oxydol ( $= 3 \text{ p.c. } \text{H}_2\text{O}_2$ ), ferric chloride and hydrochloric acid. Every 10 minutes the patient drops oxydol on to these tampons by means of a pipette, so that they are kept well soaked and the fluid can be observed in the gullet. In a few days a larger area of the nasal cavity should be ulcerated and the mucous membrane should be more hyperæmic than before. If this be not the case, the doses of iodine were too small or the instillation of  $\text{H}_2\text{O}_2$  was not performed with sufficient perseverance. If after increased doses of iodine ulceration occurs with a vividly red mucous membrane, tampons are introduced twice a day which have been soaked in 3 p.c.  $\text{H}_2\text{O}_2$  and 1 p.c. acetic acid and which are then kept moist with 2 p.c.  $\text{H}_2\text{O}_2$  and 0.5 p.c. acetic acid. After 6 to 8 weeks the granulations disappear and the ulceration heals.

J. Schaumann tried Pfannenstill's method in a case of lupus vulgaris of the palate with excellent result. He carried out the treatment with the help of a palate-protector, which left the lupoid portion of the palate exposed. Into this cavity a plug of cotton wool soaked in oxygenol ( $= 3 \text{ p.c. } \text{H}_2\text{O}_2$ ) was introduced and was renewed every hour. At the same time 0.5 gramme ( $7\frac{1}{2}$  grains) of sodium iodide was administered internally 6 times a day. In the course of a few days the majority of the tuberculous protuberances were more or less deeply ulcerated, and 4 weeks after the commencement of treatment the mucous membrane had become pale, smooth and firm. Seven months later there was not the least sign of recurrence.

A. von Reuterskiöld reports that Pfannenstill's method is also of good service in surgical cases. He obtained good results with this treatment in old wound cavities after operations for empyema and osteomyelitis, in old infected ulcers of the leg, and in the fresh operation wounds of abscesses and cellulitis.

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Schaumann, Berliner klinische Wochenschrift 1911, p. 1803. —

Almänna svenska Läkartidningen 1911, p. 731.

Reuterskiöld, Zentralblatt für Chirurgie 1911, No. 29, p. 985.

A modified method described by A. Reyn has also for its object the display of the action of iodine in a nascent state in the organism. The author was able to prove that iodine can also be liberated in the organism by electrolytic means. For this purpose 3 grammes (45 grains) of sodium iodide are given daily by mouth on an empty stomach. One to two hours after taking this dose the patient is exposed to the action of an electric current of at least 2 milliampères and 65 volts. For this purpose he holds the negative pole (a metallic plate covered with moist linen and cotton wool) in his hand, while the positive pole (one or several thin platinum-iridium needles) is passed through the skin. The current must be interrupted gradually. The current is allowed to pass for a few minutes. The method requires further elaboration, and this will probably be effected soon, as the results are very good.

R. Kaufmann describes a procedure according to which a salt of iodine and solution of hydrogen peroxide are both applied locally, but not at the same time. A 5 p.c. solution of potassium iodide and a perhydrol solution (of 0.1 to 1 p.c.  $H_2O_2$ ) were used. In obstinate subacute or chronic urethritis due to gonorrhœa small amounts of potassium iodide solution and then rather larger amounts of perhydrol solution are instilled, a form of treatment which gives very good results. The method is, however, most useful in the endoscopic treatment of suppurating lacunæ or of erosions in subacute or chronic gonorrhœa of the pars anterior urethræ, if Kaufmann's method be followed of examining with a Nitze-Oberländer urethroscope before urination. The diseased areas are first dabbed with the potassium iodide solution and a short time later with the perhydrol solution. Ten to fifteen minutes after this treatment the patient should urinate. By this method the author succeeded in a few sittings in completely curing or considerably improving very obstinate cases, which had been present for a long time and had resisted all other forms of treatment. Chronic endometritis and erosions of the cervix due to gonorrhœa were favourably influenced by this treatment. In acute gonorrhœa, however, it has so far been unsuccessful.

Reyn, *Berliner klinische Wochenschrift* 1911, p. 1873. — *Hospitalstidende* 1911, No. 40.

Kaufmann, *Berliner klinische Wochenschrift* 1911, p. 2251.

**Sodium Salicylate.**

Polain-Cartier draws attention to the excellent properties of sodium salicylate in affections of the liver, in which he was able to confirm by experiment the cholagogue action of this drug. His clinical results also show that sodium salicylate, when given in doses of 1.5 to 3 grammes (24 to 45 grains) in icterus and cholelithiasis, rapidly and permanently promotes the flow of bile. At the same time it acts as an antiseptic in the bile passages and as an analgesic. Any gastric disturbances which the drug might cause may be avoided by administering it in repeated small doses. The author also very often prescribes it in combination with sodium benzoate as follows:

Rp. Sod. salicyl.	10.0 grammes ( $\frac{1}{3}$ oz)
Sod. benz.	8.0 grammes (120 grains)
Rad. rhei. pulv.	5.0 grammes (75 grains)
Divide in p. æq. No. XX. Sig.: 3 to 6 powders to be taken daily.	

According to French authors, sodium salicylate may be employed in various forms of skin diseases. Thus Hicguet, for the treatment of herpes of the larynx and pharynx, recommends gargling with a solution of 6 grammes (90 grains) of sodium salicylate, 2 grammes (30 grains) of antipyrin and 25 grammes ( $\frac{5}{6}$  oz) of glycerin in 275 grammes (9 oz) of water. This treatment is supplemented by the prohibition of smoking, administration of aspirin, mineral waters and diuretic tea, and a suitable diet. Sodium salicylate also has a beneficial effect on the mucous membrane of the mouth; for this reason Meyer uses it to ease the pain and hasten cicatrisation after dental extractions; he introduces it into the dental cavity on a tampon. According to his experience, it may also be used in a suitable form for other diseases of the buccal mucous membrane, such as aphthous stomatitis and sublingual ulcers occurring in whooping cough, and also for dermatitis, fissures, rhagades, chilblains and cutaneous injuries; it may be used in the form of lotions or compresses (5 p.c. solution). As a substitute for borax solution it is also

Polain-Cartier, Liège médical 1911, 11<sup>th</sup> June. — Revue de thérapeutique 1911, p. 526.

Hicguet, Presse médicale 1911, p. 171.

Meyer, Klinisch-therapeutische Wochenschrift 1911, p. 744.

of service in diseases of the eye, especially in conjunctivitis occurring in a rheumatic subject.

The communications of A. Seibert are not without interest in the treatment of rheumatism. In cases of rheumatism in which the internal administration of sodium salicylate proved ineffective, he gave salicylic acid or sodium salicylate subcutaneously with excellent results. In acute rheumatism he injected every 12 hours 10 to 15 c.c., according to the severity of the case, of a freshly prepared, sterilised 20 p.c. solution of sodium salicylate for every 100 pounds of body-weight, e. g., 0.02 to 0.03 gramme ( $\frac{1}{3}$ — $\frac{1}{2}$  grain) for every pound of body-weight. To alleviate the pain caused by these injections, an injection of cocaine may, according to Seibert, be given beforehand. In chronic rheumatism the author prefers the injection of the following solution:

Rp. Acid. salicyl.	10.0 grammes ( $\frac{1}{3}$ oz)
Ol. sesam.	80.0 „ (3 oz)
Camphor.	5.0 „ (75 grains)
Alcohol.	5.0 „ (100 min.)

This solution should be sterilised before adding the alcohol. For every 100 pounds of body-weight 10 c.c. ( $\frac{1}{3}$  oz) of this solution are injected. If the cardiac weakness persists, camphor may be added up to a content of 20 per cent.

H. Gifford suggests the administration of large doses of sodium salicylate to patients suffering from sympathetic ophthalmia, who show no idiosyncrasy to sodium salicylate. Ten to thirteen grammes (150—195 grains) are given daily, and every 4 to 7 days an interval of one day is allowed. When all inflammatory symptoms have disappeared, the drug is omitted every third day, but the medication is continued for another 2 to 3 weeks. This procedure is also said to prove effective in iritis, interstitial keratitis and infections of various kinds. Atropine and inunctions are used simultaneously with the salicylate.

### Sodium Tungstate.

A new method of employing sodium para-tungstate,  $\text{Na}_{10}\text{W}_{12}\text{O}_{41}$ , for analysis has been elaborated by F. A.

Seibert, Bulletin médical 1911, 8<sup>th</sup> April. — Medical Record 1911, p. 432. — Nouveaux remèdes 1911, p. 360.

Gifford, Klinische Monatsblätter für Augenheilkunde 1910, No. 5 and 6.

Gooch and S. B. Kuzirian. They found that this salt could be advantageously used, by a simple process of ignition, in place of the preparations which had formerly been employed for the estimation of carbonates and nitrates, or of carbon dioxide and nitric acid, viz., borax, silicium dioxide, potassium dichromate and sodium metaphosphate. They prepared sodium para-tungstate by melting sodium tungstate,  $\text{Na}_2\text{WO}_4 + 2\text{H}_2\text{O}$ , with tungsten trioxide. A simpler method of forming the preparation is by melting and dehydrating commercial crystalline sodium (para) tungstate (highest purity), corresponding to the formula  $\text{Na}_{10}\text{W}_{12}\text{O}_{41} + 28\text{H}_2\text{O}$ . The dehydrated sodium para-tungstate is best kept in an exsiccator over sulphuric acid, although it is not very hygroscopic. For use, the necessary amount of sodium para-tungstate is added to about 0.5 gramme of the carbonate to be estimated (weighed exactly), which is placed in a platinum crucible. This can be approximately calculated, for, according to Gooch, 1 gramme of the salt will liberate about  $\frac{1}{10}$  of its weight of carbon dioxide. For 0.5 gramme of calcium carbonate, for example, the author used 2.5 grammes of sodium para-tungstate. After the crucible and its contents have been exactly weighed and the latter have been stirred with a platinum wire, the crucible is heated over a Bunsen burner at first at a very low temperature, then to melting point for about 5 minutes, the crucible is then placed in an exsiccator to cool. It may then be re-heated until constant weight is obtained. The difference in weight denotes the amount of carbon dioxide.

By the same procedure nitric acid is estimated in nitrates, the loss of weight indicating the amount of nitrogen pentoxide.

### Sophol.

While in chronic gono-blennorrhœa, according to previous experiences, no noticeable benefit can be expected from the use of sophol\*), the preparation has proved most useful in the prophylactic treatment of ophthalmia neonatorum. Last year it was reported upon by R. Hofstätter, A. Hör-

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Gooch-Kuzirian, Zeitschrift für anorganische Chemie 1911, Vol. 71, p. 323.

\*) Compare Merck's Reports 1906—1910.

Hofstätter, Gynäkologische Rundschau 1911, No. 11.

der, W. Hannes and A. Zeman. According to these authors, a 3 p.c. sophol solution is sufficient and only causes slight irritation of the conjunctiva, if it is always freshly prepared before use. On standing for some time it decomposes with formation of formaldehyde, which most probably gives rise to irritation of the mucous membrane of the lids. Hofstätter at first had his sophol solution freshly prepared once a week and kept it in brown glass bottles, but now he does not use solutions which are more than two days old. Care should also be paid to the suggestion that instillations of sophol solution should be carried out as soon as possible, before scabbing takes place. Zeman experimented with a 10 p.c. protargol solution and with a 2.5 p.c. sophol solution and found that both preparations give rise to the same symptoms of irritation, and possess an equally reliable prophylactic action.

### Stannous Chloride.

Two tests for burnt sugar and mallow flower colouring matter, which may be of use in the analysis of wine, have been described by A. Straub. The author uses a 1 p.c. stannous chloride solution as a reagent. If a solution containing burnt sugar of the colour of white or dessert wine be heated after the addition of 3 c.c. of stannous chloride solution and 0.5 gramme of potassium acetate until flakes of stannous oxide separate out, the latter will be coloured yellow. An aqueous extract of mallow flowers forms a greenish-blue precipitate as a result of this treatment. On the addition of mallow colouring matter to red wine which is not artificially coloured, together with the employment of suitable amounts of stannous chloride solution and potassium acetate, the colouring matter of the wine is first precipitated and on the further addition of the reagent the mallow dye can also be precipitated. According to Straub, 22 c.c. of water, 1 c.c. of stannous chloride solution and an excess of potassium acetate should be added to 3 c.c. of the dyed red wine and the mixture heated. By this test the true colouring matter of the wine is

Hörder, Münchener medizinische Wochenschrift 1911, No. 31.

Hannes, Zentralblatt für Gynäkologie 1911, No. 1.

Zeman, Gynäkologische Rundschau 1911, No. 21.

Straub, Pharmazeutische Zentralhalle 1911, p. 363.

precipitated. If the filtrate is treated in the same way with 1 c. c. of stannous chloride solution and potassium acetate, and this operation is repeated several times, after the fourth to seventh precipitation the peculiar, greenish-blue precipitate of mallow dye will be obtained.

### Sterilised Kaolin.

In the past year the kaolin treatment introduced by Stumpf was received with so much interest in medical circles, in consequence of the introduction of the sterilised kaolin preparations issued by me, that a more detailed account of it here seems called for. The chief feature of the preparations, made according to Stumpf's instructions, is to be found in the employment of a pure, uniform kind of kaolin and in its reliable sterilisation. As it was pointed out by Zweifel that non-sterile kaolin may lead to serious harm, every therapist naturally seeks to avoid this possibility. This is facilitated by using "Professor Stumpf's sterilised kaolin". It is issued in soldered tins, in the form of powder, kaolin dressings, and of kaolin compresses. The kaolin dressings are used for wounds and as tampons, the kaolin compresses for the treatment of larger wounds and transplantations. Besides these, I supply a "sterilised kaolin dressing for wounds", which is intended for immediate use for small wounds, such as are sustained by travellers, tourists, Alpine climbers, etc.

The external kaolin treatment is made very simple by the help of this kaolin dressing. It makes it possible, when necessary, to exert considerable pressure on the wound and can be applied to all parts of the body, e. g., the axilla, the perineum, between the fingers and toes. But it should be noted that it is necessary to change the dressing fairly frequently, as the kaolin, when saturated with secretion from the wound, gradually loses its protective properties. The employment of sterile kaolin powder and of kaolin dressings may be recommended as a covering over sutured wounds; for dressing all complicated wounds, which cannot be sutured until granulation occurs; as moist dressings for wounds

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Stumpf, Compare Merck's Report 1910 and the author's latest publication in the *Münchener medizinischen Wochenschrift* 1911, p. 576.

Zweifel, *Münchener medizinische Wochenschrift* 1910, p. 1787.

due to injuries, which have become dry and which easily become septic; for wounds from stabs and bullets, especially such as have already become infected and septic; for burns and malignant pustules; for infections contracted at autopsies; for suppurating blisters of the feet; for plugging the vagina, for injections in aqueous suspension for gonorrhœa in the male; for the treatment of acute vulvo-vaginitis, for ophthalmoblennorrhœa neonatorum and for all extensive wound processes, especially skin-grafts\*). In 40 to 50 p. c. aqueous suspension, sterilised kaolin is useful in the form of nasal irrigations in nasal diphtheria and hay-fever.

When kaolin is employed internally, it should also be used in a sterile form, even though the infection by pathogenic bacteria is less likely than when kaolin is applied externally. But commercial kaolin is very often wanting in those properties which are essential for the special therapeutic action of the drug. Impure preparations may also render the employment more difficult on account of unpleasant smell or taste. I reported last year on the preparation of kaolin suspensions for internal use. They are administered in Asiatic cholera, enteric processes without obstruction, and diphtheria. In cholera it is advisable to give small doses, as a single large dose would be vomited. A good method is to give a teaspoonful of kaolin suspension, which has been cooled by ice, every one or two minutes without regard to vomiting, even if it be frequent; but if the vomiting ceases or blood appears in the stools, larger amounts (100 to 150 grammes [ $3\frac{1}{3}$ —5 oz] of kaolin, or more) must be given for a dose. In obstinate vomiting dry kaolin may be tried in doses of a quarter of a teaspoonful every 1 to 2 minutes. Enteric affections, such as severe diarrhœa and vomiting, and poisoning by cheese, meat and preserved foods are treated like Asiatic cholera, if the first dose of kaolin causes vomiting. If no vomiting follows the administration of kaolin, the dose for adults may soon be raised to 200 or 300 grammes ( $6\frac{2}{3}$  to 10 oz) of kaolin, well stirred with double this amount of pure water. Babies may be given 25 to 30 grammes ( $\frac{5}{6}$ —1 oz) without fear. For every year of age 10 grammes

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\*) More exact information as to the method of using kaolin dressings is given in the directions for use and the prospectuses which accompany the original packages.

( $\frac{1}{3}$  oz) may be added to the dose, for even when large quantities of kaolin have been given internally no serious by-effects have ever been observed. In diphtheria a small teaspoonful of a 40 to 50 p.c. kaolin suspension is given every 2 to 3 minutes until the fever has subsided, after which the dose is given at intervals of 10 minutes until the membrane has disappeared. The result is evident in a few hours.

The utility of kaolin treatment is entirely confirmed in the communications of F. Schönenberger, H. Krauss, Staby, Graeser, Gallatti and Gewin. Schönenberger's remarkable results refer to the treatment of both recent, bleeding and suppurating wounds, to phlegmon, chronic eczema, ozæna, fœtor oris, suppurating bone tuberculosis, syphilitic affections, aphthous conditions, diphtheria, and hyperacidity. Graeser is also favourably disposed towards Stumpf's method in consequence of his excellent results in intestinal affections. As it is essential to begin kaolin treatment as early as possible, the author is in favour of a stock of kaolin being kept in every household, on board ship, and naturally in hospitals. Personally he has seen surprising results from the employment of kaolin in the diarrhœa of typhoid fever, diarrhœa and vomiting, and ptomaine poisoning. In the diarrhœa of typhoid fever it led to normal motions within a short time. If vomiting is present, the author advises the use of dilute suspensions which have been cooled by ice, and in desperate cases the use of morphine injections to check the vomiting. He is also of opinion that for diarrhœa and vomiting corresponding doses of kaolin suspension applied rectally might prove of service.

Staby treated amoebic and bacillary dysentery with calomel and castor oil for the first 3 days, and then with kaolin. He gave 100 grammes ( $3\frac{1}{3}$  oz) of kaolin in 300 grammes (10 oz) of water in the morning on an empty stomach. The kaolin medication proved especially favourable

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Schönenberger, Archiv für physikalische und diätetische Therapie 1910, No. 11.

Krauss, Medico 1911, p. 76.

Staby, Archiv für Schiffs- und Tropen-Hygiene 1910, No. 12.

Graeser, Jahresbericht des deutschen Krankenhauses in Neapel 1910/11, p. 36.

Gallatti, Gynäkologische Rundschau 1911.

Gewin, Nederlandsch Tijdschrift voor Geneeskunde 1911, I, p. 942.

in bacillary dysentery, in which the motions frequently became formed with surprising rapidity and the blood disappeared from the stools. The mucus in the stools also became firmer, a sign which almost always preceded a cure. A few cases of amœbic dysentery also were apparently instantly cured, but recurrences usually followed. But in the author's experience, kaolin treatment appears to have a favourable influence on the catarrh of the large intestine which accompanies dysentery.

According to Krauss, we possess in kaolin an excellent means of treatment for diarrhoea and vomiting, cholera nostras and cholera infantum. In his opinion, kaolin acts as a sedative on the intestines and envelopes the harmful bacteria to such an extent that they can do no further harm. When the desired result has been obtained, the patient may be given some rice-gruel, but nothing to drink, not even milk.

Gewin reports upon the dry treatment of leucorrhœa by Nassauer's method\*). He obtained very satisfactory results by the insufflation of kaolin powder into the vagina. Gallatti was also able to confirm the value of kaolin in the treatment of the umbilical cord\*\*).

W. Liermann combined kaolin with azodermin\*\*\*), alcohol and glycerin for the treatment of small wounds and wound surfaces, of fistulæ after appendicectomies, erosions of the cervix, remnants of the umbilical cord, eczema, herpes, intertrigo, furuncles, ulcers and hyperidrosis. This compound is used in the form of a paste, which is issued ready for use and was named by the author "kaolin wound paste". As this preparation is a most active germicide, Liermann has suggested its use for the disinfection of the hands. Its chief constituents, kaolin and alcohol, of which the latter, as is well known, has recently been generally recognised as a sovereign means for the disinfection of the hands and of the operation area, render it a promising medicament for this purpose.

\*) Compare Merck's Report 1910, p. 127.

\*\*) Compare Merck's Report 1908, p. 152.

Liermann, Deutsche medizinische Wochenschrift 1911, p. 1829 and 1884.

\*\*\*) Compare p. 168.

### Stramonium Leaves.

The investigations of Hirn and Netolitzky gave rise to grave doubt as to the medicinal value of stramonium fumigations in asthma; for these authors stated that in smoking stramonium cigarettes only minimal amounts of atropine, too minute to have any therapeutic effect, reached the smoker. As it is a matter of common knowledge that patients suffering from asthma often obtain immediate relief from the first few whiffs of a stramonium cigarette, G. Günther concluded that stramonium either acted by suggestion, or that the results of the investigations of the two workers mentioned above were incorrect. In order to settle this question he examined the smoke from large masses of stramonium leaves, and found that it contained such large quantities of atropine that the effect of the stramonium smoke must be mainly, due to the action of the alkaloid. According to his investigations, a cigarette containing 1 to 1.25 grammes of stramonium leaves gives forth, besides hydrocyanic acid, sulphuretted hydrogen and pyridine, 0.3 to 0.5 milligramme of atropine, which, on the smoke being inhaled into the lungs, may well be responsible for its action.

### Strychnine.

As a test for strychnine, Denigès modifies Malaquin's reaction\*) and suggests the following procedure. 4 c.c. of strychnine solution are added to 4 c.c. of hydrochloric acid (sp. gr. 1.19), and the mixture is heated to boiling with 2 to 3 grammes of granulated zinc. After 3 to 4 minutes the liquid is poured off. If, when cool, 1 drop of a 0.1 p.c. solution of sodium nitrite be added to 2 c.c. of this mixture, a red coloration is produced in the presence of strychnine, and the solution shows a characteristic absorption spectrum (495 and 510). The limit of sensitiveness of the reaction lies at 3:1,000,000. This reaction induced the author to

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Hirn-Netolitzky, Wiener klinische Wochenschrift 1903, p. 583. — Zeitschrift des allgemeinen österreichischen Apothekervereins 1903, p. 1454.

Günther, Wiener klinische Wochenschrift 1911, p. 748.

Denigès, Bulletin de la société chimique de France 1911, Vol. 9, p. 537.

Denigès, Journal der Pharmazie für Elsass-Lothringen 1911, p. 200.

\*) Compare Journal de pharmacie et de chimie 1909, II.

investigate the reduced strychnine solutions in greater detail, with regard to their utility as reagents. It is well known that on the reduction of strychnine by hydrogen, tetra-hydro-strychnine and strychnidine are produced; these are coloured red by oxidising substances. The author therefore prepared a reagent (which he calls hydro-strychnine solution) according to the following method. 5 c.c. of a 1 p.c. strychnine sulphate solution are mixed with 5 c.c. of hydrochloric acid (sp. gr. 1.19), 5 grammes of granulated zinc are added, and the mixture is heated to boiling, left to stand for 10 minutes, cooled and poured off from the undissolved zinc. This reagent is coloured red by traces of bromine, and the mixture shows an absorption spectrum in the yellow at 550, whereas iodine does not react in the same way. Other oxidising agents, such as ferric chloride, chromic acid, permanganic acid, nitric acid and nitrous acid, also give rise to a red coloration, but to an absorption spectrum at 495 and 510. The sensitiveness of the reaction lies at 1 part of bromine in 100,000 parts of water. By means of the same hydro-strychnine reagent the presence of nitrates and nitrites can be demonstrated in water. If the reagent is added to drinking water which contains nitrites (10 c.c. of water and 0.5 c.c. of reagent), the mixture is coloured pink to dark red, according to the amount of nitrous acid present. Nitrates cause no coloration, or only if the solution be mixed with half its volume of sulphuric acid before the addition of the reagent. The reaction described is also said to be suitable for the colorimetric estimation of nitrous acid.

Another reagent is, according to Denigès, the so-called "ammonium strychno-molybdate", which is obtained by mixing strychnine sulphate solution (0.5 c.c. in 80 c.c. of water), 10 c.c. of nitric acid (sp. gr. 1.4) and 10 c.c. of Sonnenschein's ammonium nitro-molybdate solution. The reagent is said to serve for the demonstration of phosphoric acid, as it gives a precipitate with phosphates.

### Strychnine Cacodylate.

This preparation is still used therapeutically, although it shows no advantages over other strychnine salts. An aqueous solution 1:100, such as is usually used for subcutaneous injection, cannot readily be prepared, as the strychnine base

separates either immediately or in a very short time. For cacodylic acid is much too feeble an acid to keep strychnine in solution in such great dilution. Therefore anyone who cannot dispense with the use of strychnine cacodylate for any reason, must be satisfied with an aqueous or oily suspension of the preparation. But as the action of the drug is most probably entirely dependent upon its strychnine component, it will be much better to use the readily soluble strychnine salts (sulphate, hydrochloride, nitrate, etc.). In the minute doses in which strychnine cacodylate is administered, the cacodylic acid component can scarcely have any effect. When giving the maximum dose, about 0.0015 gramme ( $\frac{1}{40}$  grain) of cacodylic acid is taken, an amount of which the value is quite hypothetical, for as a rule 100 times this dose is prescribed. But if it be desired to administer simultaneously strychnine and cacodylic acid, then strychnine sulphate and sodium cacodylate in aqueous solution may be injected separately, and in the desired dose. They cannot be given together in one solution, as the two salts on coming together in aqueous solution form sodium sulphate, strychnine and cacodylic acid, and the strychnine, on account of the difficulty with which it dissolves, separates out in a crystalline form.

Consideration must also be given to the dosage of strychnine cacodylate, as the German Pharmacopœia has reduced the maximum dose of strychnine (or strychnine nitrate) by one half. As I have already pointed out elsewhere\*), Eysseric, in the treatment of tuberculosis, injected daily doses up to 0.036 gramme, viz., up to 3.6 grammes of a solution 1:100. Taking into consideration the dose given in the present German Pharmacopœia, this represents  $3\frac{1}{2}$  times the maximum dose, the prescribing of which therefore calls for care and reflection. The maximum dose fixed by law in Germany is 0.005 gramme for a single dose, and 0.01

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\*) Merck's Reports 1902, p. 8 and 1910, p. 36. Compare also 1907, p. 234. — The dosage given in Merck's index 1910, p. 392 contains a printer's error. It should read: max. single dose 1.0 and max. daily dose 2.0, instead of 0.1 and 0.2, of the solution 1:100, as in 1 or 2 grammes of this solution the maximum dose is contained, as laid down in the Pharm. Germ. IV. According to the Pharm. Germ. V., the maximum doses of the 1 p.c. solution should be reduced to 0.5 and 1.0.

gramme for the total daily dose of strychnine nitrate. (The maximum single and daily doses for strychnine, or its salts, are, according to the Pharm. Austr., 0.01 gramme and 0.02 gramme, Pharm. Dan., 0.005 gramme and 0.01 gramme, Pharm. Franç., 0.005 gramme and 0.015 gramme, Pharm. Helv., 0.01 gramme and 0.02 gramme, Pharm. Hungar., 0.01 gramme and 0.02 gramme, Pharm. Ross., 0.003 gramme and 0.01 gramme, and Pharm. Ital., 0.005 gramme and 0.015 gramme.)

### Sulphoform.

Sulphoform (triphenylstibine sulphide) was tried by W. Schneider in 10 p.c. oily solution\*) for alopecia pityrodes. The method of employment was that suggested by M. Joseph. Above all, the author points out that the preparation is easier to handle and pleasanter to use than are the usual ointments which contain sulphur, for which reason his patients consented more readily to a sulphoform cure. The results were on the whole satisfactory, though not in every case. Generally the loss of hair and formation of scales were diminished or completely inhibited. Unsatisfactory results may be expected if the patients have not the necessary patience for carrying out the cure, or if the disease has so deeply penetrated the scalp that medication has become useless. But in suitable cases a trial may well be recommended, as sulphoform is said to be free from irritant effects.

### Syrgol.

Syrgol, which was introduced by Kollbrunner for the treatment of urethral gonorrhœa, was tested by C. A. Hegner with regard to its value in conjunctivitis. At first he tried it in ophthalmia neonatorum and adutorum. The action is here apparent in the rapid decrease of the inflammatory symptoms, of the swelling of the lids and conjunctiva, and in the rapid disappearance of the gonococci. In a few cases of ophthalmia neonatorum a cure was effected

Schneider, Dermatologisches Zentralblatt 1911, No. 7 — Excerpta medica 1911, Vol. 21, p. 91.

\*) Compare Merck's Report 1910.

Joseph, Dermatologisches Zentralblatt 1910, No. 1 and 2. — Merck's Report 1910, p. 358.

Kollbrunner, Merck's Report 1909, p. 328.

Hegner, Münchener medizinische Wochenschrift 1911, p. 1726.

by means of syrgol alone in the course of a week, generally a complete cure was obtained after 1 to 2 weeks, while only in exceptional cases were gonococci found at the end of a fortnight. Syrgol also proved of service in suppurative conjunctivitis not due to gonorrhœa, and in the conjunctivitis occasionally following operations for cataract, in which the muco-purulent secretion is an annoyance to the patient. Both swelling and secretion often disappeared in these cases after 1 to 2 days of treatment.

In recent gonorrhœa, in which gonococci are present, a 5 p.c. syrgol solution is instilled into the conjunctival sac 2 to 6 times a day, and the eyes are cleared from secretion from time to time by means of boric acid solution. Other forms of purulent conjunctivitis may be treated with a 2 p.c. solution.

The author was able to observe its influence on affections of the lachrymal sac in two cases. One was a case of acute dacryocystitis with swelling, redness and acute sensitiveness in the region of the lachrymal sac. The lachrymal sac was irrigated daily with a 1 p.c. solution of syrgol, and in a week the patient was cured. In the same way the secretion ceased in a few days in a case of non-inflammatory suppuration of the lachrymal sac.

### Tannoform.

The good results which have attended the use of tannoform by Zieger in vaginal affections and diseases of the uterus in cows, and by Fuchs in septic metritis of cows, induced F. Westerling to try the drug in the treatment of very severe chronic endometritis in 3 mares. For this purpose he prepared bougies consisting of 20 grammes ( $\frac{2}{3}$  oz) of tannoform and 15 grammes ( $\frac{1}{2}$  oz) of cacao butter. After irrigation of the uterus by means of an antiseptic fluid, one of these tannoform bougies was introduced into the uterus.

The first mare was treated three times, leaving an interval of one day between each application. The exudate, which was cleared out by the irrigation and was at first muco-purulent

Zieger, Berliner tierärztliche Wochenschrift 1901, No. 29. —

Merck's Report 1901, p. 164.

Fuchs, Tierärztliches Zentralblatt 1902, No. 10.

Westerling, Österreichische Wochenschrift für Tierheilkunde 1911, No. 25.

and green, became more fluid, and light yellow in colour. Later on the animal was only treated twice a week; at the end of 4 weeks, after 11 applications, it was discharged perfectly well. At the last application it was barely possible to introduce the nozzle of the irrigator into the uterus; this could only be done after manual dilatation of the cervical canal. The 0.5 p.c. bacillol solution used for irrigation was as clear on flowing out as on its introduction.

The other two mares were treated with equal success. There were no recurrences.

### **Tannyl.**

In the diarrhoea of distemper of dogs, tannyl\*) has proved a reliable intestinal astringent and antiseptic. It is, according to Deckert, preferable to opium in that it is odourless and tasteless and does not therefore cause the animals to vomit. He administered the preparation, according to the size of the dogs, in single doses of 1 to 2 grammes (15—30 grains), and in daily doses of 2 to 6 grammes (30—90 grains). Tannyl cannot effect the cure of distemper, and fresh attacks of diarrhoea may occur. Now and again the drug fails, but on the whole it is very useful and prevents too great a loss of strength. In all other intestinal diseases, partly of unknown origin and non-infectious in nature, tannyl exhibits a most reliable action.

### **Tartarated Antimony.**

Like other observers\*\*), Morgenroth was able to confirm the potent and rapid curative action of tartar emetic on mice infected with trypanosoma Brucei. He only observed a slight degree of resistance in the trypanosomes to antimony. Tantalum, which is chemically nearly related to antimony has, according to the author's investigations, no trypanocidal action and under certain conditions is even capable of neutralising the curative effect of antimony.

According to G. Klemperer, tartar emetic is of value in pernicious anæmia. He gave a subcutaneous injection of 0.001 gramme ( $\frac{1}{64}$  grain) daily for 20 days with good result.

\*) Compare Merck's Reports 1908—1910.

Deckert, Berliner tierärztliche Wochenschrift 1911, p. 959.

\*\*) Compare Merck's Report 1908.

Morgenroth, Deutsche medizinische Wochenschrift 1911, p. 334.

Klemperer, Deutsche medizinische Wochenschrift 1911, p. 334.

Grimme discusses the use of tartar emetic against ascarides in veterinary practice. His experience with this drug leads him to the conclusion that the tartar emetic treatment of ascaridiasis in horses will gain many adherents when more attention has been paid to the dosage of the preparation. He himself prescribed for full-grown horses and strong 2 to 4-year-old foals 15 to 20 grammes ( $\frac{1}{2}$ — $\frac{2}{3}$  oz), for one-year-old foals 10 grammes ( $\frac{1}{3}$  oz), and 5 grammes (75 grains) for animals 6 months old. Sucking foals were given 2 grammes (30 grains). To avoid toxic symptoms he always gave these amounts in several doses and never observed symptoms of intoxication, even when the separate doses followed one another at short intervals. In order to render the action of the drug as complete as possible, he withdrew on the evening before the treatment the water from horses and especially from foals which were not addicted to drinking much. On the following morning the tartar emetic was administered in a bucketful of water (or less water for small doses), so that a third of the solution was given to the horse at 6 o'clock, a third at 7 o'clock and a third at 8 o'clock. It was not fed until 8-30 a. m. Purgatives, according to Grimme, are not usually required. The action of the drug is assisted by previous and simultaneous feeding with turnips and bran.

### Tests for Blood.

The reliability of tests for blood is still limited, and it is the aim of analytical chemists to improve the methods at present in use and to render them specific. Last year various papers on this subject appeared, the further investigation of which can but be useful.

One of the most reliable tests for blood is undoubtedly benzdine (but only one special quality, which is on the market under the name of "benzdine for blood tests", whereas benzdine puriss. is of no use for this purpose), and this is confirmed by T. Gigli. The author used a solution of 1 gramme of benzdine in 2 grammes of acetic acid, a few drops of which he placed upon the stains to be tested and then added a little 3 p. c. solution of hydrogen peroxide. A

blue coloration indicates the presence of blood. (Compare Merck's Reports 1906—1910.)

I. Boas, C. Sartory, P. A. Kober, R. Goldschmidt and G. Rivat report upon the phenolphthalein reaction. Boas at first used the so-called Meyer's reagent as a test for occult bleeding from the gastro-intestinal canal. It is obtained by dissolving 2 grammes of phenolphthalein and 20 grammes of fused potassium hydroxide in 100 grammes of water and reducing the solution by warming with 10 grammes of zinc dust. Later he only used 1 gramme of phenolphthalein and 25 grammes of potassium hydroxide for the preparation of this colourless reagent. In order to carry out the test, the excrement to be tested is mixed with water, extracted with ether and the ether added to 20 drops of the reagent. A positive reaction is recognised by adding 3 to 4 drops of  $\text{H}_2\text{O}_2$  (3 p. c.), when the reagent turns red. This method is a reliable one for the demonstration of blood in the fæces; as regards sensitiveness, it is entitled to be placed between (Weber's) guaiacum test and the benzidine test. In dealing with large amounts of blood the addition of  $\text{H}_2\text{O}_2$  is, according to Goldschmidt, unnecessary. In contradistinction to Boas and Goldschmidt, Kober asserts that Meyer's reagent is not suitable as a blood test, as it contains phenolphthalates which might interfere with its specificity. This possibility may best be avoided by only using a reagent which does not turn red on dilution with water. Sartory also insists that Meyer's reagent should be used to supplement other blood tests and that it cannot be described as absolutely reliable. Therefore, in order to render the test more specific, Rivat uses albuminate of manganese as a catalytic agent. In his opinion, this is changed in the alkaline reagent into colloidal manganese oxide, which carries the oxygen from the oxyhæmoglobin of the blood to the phenolphthalin. The latter, when oxidised to phenolphthalein, is coloured red by the alkali which is present. In carrying out the test, as little manganese albuminate as possible should be used, as this is turned brown by the alkali and may conceal the red coloration. Therefore 2 drops

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Boas, Deutsche medizinische Wochenschrift 1911, p. 62.

Sartory, Klinisch-therapeutische Wochenschrift 1911, p. 1114.

Kober, Deutsche medizinische Wochenschrift 1911, p. 1481.

Goldschmidt, Deutsche medizinische Wochenschrift 1911, p. 1347.

Rivat, Lyon médical 1911, 15<sup>th</sup> October.

of the reagent and 1 drop of a 0.5 p. c. manganese albuminate solution are added to the solution to be tested. If blood be present, the mixture is almost immediately coloured rose-red, and in the course of a minute becomes violet-red.

A modification of van Deen's (guaiaicum-resin-turpentine oil) test\*) is described by Wackers. It consists of shaking up the urine to be tested with some kieselguhr and pouring it on to a filter. When the fluid has filtered through, the reagent is poured on to the filter; it is prepared by shaking up equal parts of ozonised turpentine oil and a freshly prepared, brown, alcoholic solution of guaiaicum resin. If the reaction be positive, the filter will be coloured an intense blue within 45 seconds at the latest. The reaction is said to be extremely sensitive. In order to avoid error the urine may be boiled before carrying out the test, as by this means other substances than blood lose their capacity for colouring the reagent. With this precautionary measure the ethereal extract of fæces may be used for this filter test.

Gerlach, for the recognition of traces of blood, used the modification of the guaiaicum-resin-turpentine oil reaction suggested by Florence, which consists in adding pyridine. If not more than a quarter of the volume of pyridine be added, the appearance of the result is hastened and the reaction itself intensified. This addition is said to eliminate several sources of error in van Deen's test. P. Spehl and A. Müller have attempted to increase the value of the test by using a specially prepared tincture of guaiaicum. Spehl always prepares his tincture freshly by shaking up finely powdered guaiaicum wood with alcohol. 4 c. c. of this are mixed with 1 c. c. of sodium carbonate solution (20 p. c.), 4 c. c. of  $H_2O_2$  (3 p. c.), and 1 c. c. of alcohol (96 p. c.). Stomach contents and urine, after the addition of acetic acid, are shaken up with a few c. c. of ether and the ether is then added to an equal quantity of the above mentioned mixture. Traces of hæmoglobin are said to cause a distinct blue or greenish-blue coloration. Müller prepares tincture of guaiaicum as follows: 5 grammes of guaiaicum resin are dissolved in 10 c. c. of glacial acetic

Wackers, Münchener medizinische Wochenschrift 1911, p. 197.

\*) Compare Merck's Reagenzien-Verzeichnis 1908, p. 55.

Gerlach, Ärztliche Sachverständigen-Zeitung 1911, No. 13.

Spehl, Journal médical de Bruxelles 1911, No. 14.

Müller, Pharmazeutische Zeitung 1911, p. 555.

acid and 10 c.c. of alcohol and diluted with double the volume of water. The tar-like substances which separate out, and which are blamed by some for the causation of errors in van Deen's test, are filtered off and the filtrate is slowly poured into about 100 c.c. of boiling water. As the mixture cools a resinous substance separates out; the aqueous fluid is poured off; the resinous substance is freed by washing from the yellow sediment and is dissolved in 10 times the amount of alcohol (90 p.c.). In order to carry out the test for blood, a mixture of 20 c.c. of this guaiacum tincture and 1 c.c. of perhydrol is used.

Another test for blood, which is very sensitive and in a high degree specific and which may prove of great value for forensic purposes, is recommended by O. von Fürth. To avoid errors, the author combined Adler's test\*) with the method described by O. Leers. He extracts the hæmoglobin from the substances to be tested by means of caustic potash solution and pyridine, by which method other disturbing substances are not extracted, and with this extract he carries out Adler's test. As a reagent he uses a solution of 1 gramme of leuco-Malachite green base in 50 c.c. of glacial acetic acid, diluted with water to 500 c.c. To render the solution colourless it is shaken up with chloroform, which takes up the green colouring matter. The test is carried out by pouring the pyridine solution, which has been used for the extraction, on to filter paper and adding a little of the colourless leuco-Malachite green reagent, which has been mixed with 1 p.c.  $H_2O_2$ . A green coloration of the paper indicates the presence of blood.

#### Tetranitromethane.

Tetranitromethane\*\*),  $C(NO_2)_4$ , is at the ordinary temperature a heavy yellow oil, which boils at  $126^\circ C$ . with slight decomposition. If cooled below  $13^\circ C$ . the preparation gradu-

Fürth, Zeitschrift für angewandte Chemie 1911, p. 1625.

\*) Compare Zeitschrift für physiologische Chemie 1904, Vol. 41, p. 59.

Leers, Die forensische Blutuntersuchung, Berlin 1910, p. 27.

\*\*) Compare Schischkow, Liebigs Annalen Vol. 119, p. 248. — Chattaway, Journal of the Chemical Society 1910, Vol. 97, p. 2099 and Chemical News 1910, Vol. 102, p. 307. — Berger, Comptes rendus de l'académie des sciences 1910, Vol. 151, p. 813.

ally solidifies, forming crystals. The crystals melt at 13° C. Tetranitromethane is insoluble in water.

According to I. Ostromisslensky, tetranitromethane is a reagent with the help of which ethylene compounds are readily demonstrated. If a few drops of this reagent are added to a neutral or acid solution of any substance, in the presence of ethylene compounds a yellow, orange or brownish coloration will immediately appear. In alkaline solution tetranitromethane is decomposed with the formation of yellow nitroform salts, for which reason the reaction should not be attempted in alkaline solution. The author mentions a large number of bodies which give a colour reaction with tetranitromethane. The following are examples: ethylene = light yellow, hexylene = yellow, turpentine oil = reddish yellow, allyl alcohol = orange-yellow, eugenol = brownish-red, cholesterin = light yellow, aceto-acetic ester = light yellow, benzol and its homologues = light yellow, naphthalene = orange-red, coumarin = canary yellow, vanillin = orange-yellow, anisol and phenetol = intense red, etc. The reaction of the ethylene bodies with tetranitromethane is said to be very sensitive and therefore suitable for the demonstration of these bodies in urine, methyl alcohol and technical products.

Tetranitromethane is a feeble oxidising agent; it oxidises hydroquinone in alcoholic solution to quinhydron, and dimethyl-anilin in carbon disulphide to crystal violet.

### Theobromine.

Theobromine treatment has, according to Ch. Andry, proved useful in avoiding poisoning by mercury. This communication is of special interest, as intoxications through this metal occur with comparative frequency on account of its widespread use. In 3 very severe cases the author observed a rapid improvement in the symptoms following the administration of a daily dose of 3 to 4 grammes (45 to 60 grains) of theobromine. The action of the drug most probably depends upon its diuretic effect, in consequence of which the mercury or its salts are more rapidly eliminated. Possibly theobromine may be of use as a prophylactic.

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Ostromisslensky, *Journal für praktische Chemie* 1911, Vol. 84, p. 489.

Andry, *Annales de dermatologie* 1911, p. 286.

### Thiocyanates.

In order to settle the question as to the toxicity of the thiocyanates\*), Fr. Franz carried out detailed pharmacological investigations. His results were as follows: Alkaline thiocyanates, given to rabbits, guinea-pigs, dogs and cats exerted no action referable either to the liberation of prussic acid nor to the thiocyanate ion. On the whole, the symptoms which have been observed appear to be due to salt action, but the thiocyanates themselves cannot be regarded as poisons in the ordinary sense. While in rabbits and guinea-pigs, which are known to possess a thin stomach wall which offers comparatively little resistance to salt solutions, and are unable to vomit, internal doses of 0.5 to 0.9 gramme of an alkaline thiocyanate proved fatal in the course of 6 hours to 4 days, dogs and cats merely vomited after the internal administration of thiocyanate. Following the subcutaneous injection of 1 gramme of potassium thiocyanate in dogs weighing 7 to 8 kilogrammes, the animals showed no symptoms of poisoning whatever. In rabbits and guinea-pigs corrosion of the stomach was observed, and therefore the toxic action of the thiocyanates may be due to their caustic properties. But these observations made on rodents cannot be taken as a proof of toxicity for human beings; rather may it be assumed that the alkaline thiocyanates are no more poisonous for human beings than for dogs or cats, which would agree with other observations published in the literature.

### Tincture of Coca.

It is well known that cocaine occasionally proves useful in vomiting and sea-sickness; it is therefore not surprising to hear that tincture of coca has the same effect. According to C. Beer, doses of 12 to 15 drops, administered several times a day, are said to lead to the cessation of nausea and vomiting, even in obstinate cases, and to improve the appetite. In the author's opinion, the alcohol of the tincture as well as the cocaine take part in this action. He has found tincture of coca to be a pleasant and rapidly acting medicine. It must be remembered that tincture of coca, like cocaine, only

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\*) Compare Merck's Report 1910, p. 362.

Franz, Arbeiten aus dem kaiserl. Gesundheitsamte, Vol. 38, No. 4.  
Beer, Therapeutische Monatshefte 1911, p. 724.

exerts its favourable influence on the gastric symptoms of sea-sickness, and can thus only be regarded as a palliative. According to the cerebral theory of sea-sickness, recently put forward by E. Schepelmann, all attempts at treatment aimed at the stomach, circulatory system, etc., must fail, as their general action is wanting. The endeavour to reduce the irritability of the cerebral cortex is only supported by means of an efficacious sedative, such as is found in veronal, rather than in the modern bromine preparations. A sedative which acts rapidly and with certainty in the majority of cases succeeds in suppressing or at any rate mitigating sea-sickness\*).

### **Tiodine.**

After M. Weiss and A. Zweig had experimented with tiodine (thiosinamin-ethyl-iodide) with some degree of success in parasyphilitic diseases of the central nervous system, F. Patschke tested this preparation in arterio-sclerosis of the central nervous system. It was administered subcutaneously 3 times a week in doses of 0.2 gramme (3 grains), a course of 16 to 20 injections being given. They are said to be quite painless and to cause no local symptoms of irritation. The author found that by means of this treatment the subjective symptoms, such as headache and vertigo, were rapidly improved, while other symptoms, such as paræsthesia, burning sensation in different parts of the body, etc., were less favourably influenced. In 3 cases, in which the psychical symptoms were more prominent, the other troubles were alone improved, but not the absent-mindedness and depression. On the whole, the author considers it advisable to use tiodine in arterio-sclerotic diseases of the central nervous system, as it is free from danger while being efficacious; it may be especially recommended in those cases in which previous prolonged iodine medication has been without effect.

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Schepelmann, *Klinisch-therapeutische Wochenschrift* 1911, p. 1499.

\*) Compare Merck's Report 1907, p. 254 and 1910, p. 372.

Weiss, *Wiener medizinische Wochenschrift* 1907, No. 7. — Merck's Report 1907, p. 246.

Zweig, *Deutsche medizinische Wochenschrift* 1908, p. 457.

Patschke, *Deutsche medizinische Wochenschrift* 1911, p. 1513.



of lupus Pick also obtained a very good result; he administered 10 drops of a 0.25 p.c. titanium salicylate solution internally 3 times a day and painted the parts with the same solution, as well as applying a 3 p.c. titanium salicylate solution in the form of an ointment. In pulmonary phthisis sprays of a 0.25 p.c. titanium solution and the internal administration of titanium salicylate solution (in teaspoonfuls) are said to have proved very useful.

### **Tribromo- $\beta$ -Naphthol.**

Tribromo- $\beta$ -naphthol,  $C_{10}H_4Br_3OH$ , forms a greyish-white, crystalline powder, melting at  $155^{\circ}C$ . It dissolves readily in alcohol, ether, benzol, acetone and alkalies. According to Lehmann's communications, the 0.5 p.c. alcoholic solution of this preparation has proved most useful as a disinfectant for the hands. But some of the persons who made use of this solution were affected 4 weeks later with an urticarial rash, which the author attributes to a contamination of the commercial tribromo-naphthol. The likelihood of this assumption is increased if a brownish-red preparation be used, such as has several times been described in the literature\*).

### **Trichloroacetic Acid.**

In place of carbonic acid snow\*\*), G. Knauer uses trichloroacetic acid for small warts or keloids, the application of which is said to be technically simpler and to require less practice than does cauterising with solid carbonic acid. Another advantage of trichloroacetic acid lies in the fact that it can be applied by means of small pointed glass rods, made for the purpose, to minute new growths, without causing harm to the adjoining skin. It is generally sufficient to apply the acid quite gently, but its cauterising power can be much increased by pressing and kneading the wart with the glass rod, so that as a rule a single application suffices. But if a repetition be necessary, it is best to wait until the scab has come away. Care should be taken in applying the acid

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Lehmann, Beiträge zur klinischen Chirurgie 1911, Vol. 47 (Festschrift für L. Rehn).

\*) Pharmazeutische Zeitung 1911, p. 654. — Vierteljahresschrift für praktische Pharmazie 1911, p. 123.

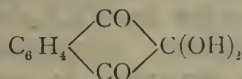
\*\*) Compare p. 190 of this Report.

Knauer, Münchener medizinische Wochenschrift 1911, p. 512.

only to touch the new growth and to spare the healthy skin. Whoever has not the necessary experience may protect the healthy skin by means of collodion, or have a little pad of cotton wool in readiness, with which to remove any superfluous acid at once. The action of the acid, if desired, can be modified by varying its concentration. As the aqueous solution of the acid keeps indefinitely, a concentrated solution (10 parts of acid and 1 part of water) can be kept in stock and used undiluted or diluted as occasion requires. It is also convenient to dissolve a few crystals of the acid in a few drops of water in a watch glass before use; this is quickly done, because the preparation is very hygroscopic. In suitable cases a small crystal may be allowed to dissolve on the new growth, as was done by Sytschow in cauterising the larynx in the treatment of tuberculous laryngitis. This treatment must be carried out with the utmost care, in order that the crystal may not fall into the trachea. Sytschow first paints on a solution of 1 gramme (15 grains) of cocaine hydrochloride, 0.05 gramme ( $\frac{3}{4}$  grain) of carbolic acid and 0.5 gramme ( $7\frac{1}{2}$  grains) of antipyrin in 10 grammes ( $1\frac{1}{3}$  oz) of water, and then applies the acid in the form of fine crystals by means of a sound. By this method it is said not to flow about so much as when aqueous trichloroacetic acid is used, and also to act more deeply. It cleans and cicatrises the ulcers and forms a scab which protects the ulcerated surface from re-infection. The cauterisation causes no pain and engenders no complications or inflammatory symptoms, as does the cauterisation by means of the galvanocautery.

### **Triketohydrindenehydrate.**

Triketohydrindenehydrate, first prepared by S. Ruhemann, and having the formula



Sytschow, *Zeitschrift für Laryngologie* 1911, No. 5. — *Zentralblatt für die gesamte Therapie* 1911, p. 359. — *Deutsche Medizinal-Zeitung* 1911, p. 458.

Ruhemann, *Journal of the Chemical Society* 1910, *Transactions* II, p. 1438 and 2025.

forms colourless crystals, soluble in water and alcohol, which reduce Fehling's solution strongly on heating. The preparation, as far as I know, has not as yet been put on the market, but as it may prove of interest in physiological investigations, it may be pointed out that its discoverer found that the preparation might be used as a test for albumins. E. Abderhalden and H. Schmidt have recently investigated this compound. Their results show that triketohydrindenehydrate in neutral solution gives a more or less intense blue coloration with albumins, peptones, polypeptides and  $\alpha$ -amido-acids (with the exception of prolin, oxyprolin and pyrrolidon-carbonic acid). The skin is also coloured blue by the reagent. In carrying out the test, the authors state that a solution of 0.1 gramme of triketohydrindenehydrate in 30 or 40 c.c. of water should be used. 1 to 2 drops of this solution are added to 1 c.c. of the liquid to be tested and the mixture is heated to boiling for a short time. The positive reaction, i. e., the blue coloration, becomes evident as it cools. The neutral reaction of the liquid is of great importance for the result of the test. If the reaction be acid, the blue coloration which appears has a more or less definite reddish tinge, or the colour may not appear at all. An alkaline reaction entirely prevents the appearance of the coloration. The authors intend to make further investigations of these colour reactions and their value as a test for albumins and their products of decomposition in the body fluids.

### **Tropacocaine Hydrochloride.**

Spinal anæsthesia by means of tropacocaine is fully discussed by R. von Hippel in an exhaustive paper on the modern methods of treating pain in surgery. As it really contains nothing new and may be looked upon as a confirmation of the data to which I have referred in my Reports in the course of the last few years\*), I shall merely refer here to this interesting publication. Tropacocaine is at the present time fairly universally recognised by surgeons to offer the best means for producing spinal anæsthesia, but it may be

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Abderhalden-Schmidt, Zeitschrift für physiologische Chemie 1911, Vol. 72, p. 37.

Hippel, Fortschritte der Medizin 1911, p. 175.

\*) Compare Merck's Reports 1896—1910.

news that the spinal application of the drug is also of use outside the sphere of surgery. According to a communication by Sapatsch-Sapotschinsky, the spinal application of tropacocaine is said to have proved of value in a series of cases of gastric crises in tabetic subjects. This treatment deserves special consideration when morphine does not alleviate the tabetic pains. For this purpose, the author withdrew 2 c.c. of cerebro-spinal fluid and injected an equal quantity of tropacocaine solution, in order to avoid an increase in the cerebro-spinal pressure. After the injection the patients had to remain for about 5 hours in a semi-recumbent position. The cutaneous anæsthesia produced by this method only reached as far as the nipple and lasted for about 24 hours.

G. Lichtenstern reports upon the employment of tropacocaine in veterinary surgery, with special reference to its utility in infiltrations of the eye-ball in horses. After disinfecting the site of injection by means of tincture of iodine, the author injected 10 to 30 c.c. ( $\frac{1}{3}$ —1 oz) of a 2.5 to 10 p.c. solution of tropacocaine in close proximity to the eye-ball; he introduced the needle about  $1\frac{1}{2}$  cm. aborally from the arcus orbitalis in the sagittal plane of the supra-orbital foramen, and directed it towards the third upper premolar of the opposite side. When the needle has entered the periorbital space, which according to the author gives the sensation of perforating a drum-skin, the tropacocaine is injected. The depth and extent of anæsthesia are proportionate to the amount injected. By vigorous massage at the site of injection and of the eye-ball, anæsthesia is produced in 3 to 5 minutes and lasts for 20 to 30 minutes, it is accompanied by mydriasis and exophthalmos. As the anæsthesia thus produced affects the entire eye-ball, every sort of operation on the eye-ball may be carried out under its influence, notably enucleation of the eye-ball. Tropacocaine applied by this method is specially to be recommended, because the employment of large doses is only possible with relatively non-toxic drugs such as tropacocaine. Even on using 2 grammes (30 grains) of tropacocaine for a horse, the author observed no symptoms of intoxication.

Sapatsch-Sapotschinsky, Russkij Wratsch 1910, No. 31.

Lichtenstern, Münchener tierärztliche Wochenschrift 1911, No. 21 und 22.

### Trypsin.

Jochmann, W. Bätzner and M. Brandes have fully discussed trypsin treatment in surgical tuberculosis. Jochmann recommends it for cold abscesses, tuberculous fistulæ, suppurating lymphatic glands, ulcers of the soft tissues, hygroma of the tendon sheaths, tuberculosis of the joints and fistulo-purulent synovial tuberculosis. The treatment consists in removing the pus from the cold abscesses by means of a trocar or aspirator and injecting a 1 p.c. trypsin solution (1 to 2 c.c.) into the abscess cavity. Puncture and injection can be painlessly carried out under ethyl chloride. Should the pus be so thick that its removal causes difficulty, the trypsin is injected into the closed sac, which is not punctured for 1 to 2 days, when the pus has become more fluid through the action of the trypsin. While occasionally one injection suffices for abscesses, several injections are always required for fistulæ and must be repeated at intervals of 5 to 6 days. Ferment therapy is also of service in caries of the ribs and of the vertebræ, and in tuberculous, suppurating lymphatic glands; the cosmetic results are better than those obtained by operative treatment. But the best results are obtained in tuberculous hygroma of the tendon sheaths. Local and general reactions are comparatively rarely observed and only in isolated cases are they so severe that the site of injection becomes red, swollen, œdematous and is hot to the touch. These symptoms, which are accompanied by pain and fever, usually subside in 2 to 3 days\*).

The results obtained by Bätzner by means of the ferment treatment in the conditions mentioned above are also unequivocal and promising. He considers that trypsin would form a good substitute for iodoform treatment, as a smaller volume of trypsin is necessary for an injection, and the action takes place more rapidly and lasts longer than is the case with iodoform injections. The danger of poisoning is also said to be less than by the use of iodoform, while the patient can be up and about during the treatment with trypsin. The fact is also noteworthy that severe, fistulo-purulent bone and joint diseases can be cured by the use of trypsin injections alone.

Jochmann, Zeitschrift für ärztliche Fortbildung 1911, No. 3.

Bätzner, Archiv für klinische Chirurgie 1911, Vol. 95, No. 1.

Brandes, Münchener medizinische Wochenschrift 1911, No. 28.

\*) Compare Merck's Report 1910.

Brandes would not like to dispense with the use of trypsin in the conservative treatment of surgical tuberculosis, although his experience does not lead him to expect much from it. Although he always observed typical liquefaction of the pus after the injection of trypsin, and in some cases the superiority of trypsin over iodoform was apparent, yet he considers iodoform injections to be the best form of treatment, as their value depends not only upon the development of a simple bactericidal action, but also upon an indirect ferment action engendered by leucocytactic energy.

### Ureabromine.

Ureabromine (bromo - calcium urea), of the formula  $\text{Ca Br}_2 \cdot 4\text{CO}(\text{NH}_2)_2$ , occurs either as colourless and odourless crystals, or as a white powder. It contains 36 p.c. of bromine, and is readily soluble in water and in alcohol. Melting point  $186^\circ \text{C}$ . It has a cooling and somewhat bitter taste.

Ph. Fischer and J. Hoppe, on investigating this preparation, found that it is not only readily absorbed, but that it also enriches the blood in lime salts. Its influence on increased muscular irritability could be demonstrated. But it has not been decided whether this effect should be attributed to the bromine or to the calcium. This point was especially investigated in children suffering from epilepsy, spasmodic conditions, or rickets. When the normal calcium content of the blood had once been reached, variations in the amount of calcium occurred after about 5 to 6 weeks; it generally exceeded the normal, whereupon there was a return of the former muscular irritability. It follows that ureabromine should not be given continuously in these conditions, as its good effect only lasts for a short time (6 to 8 weeks), and it is better to replace it for a time by the use of alkaline bromides. Ureabromine medication also has a beneficial effect on epilepsia electrica and the status epilepticus. Ureabromine is prescribed with a mixed diet as follows: Rp. Ureabromine 40.0 grammes ( $1\frac{1}{3}$  oz), Aq. destill. 300.0 grammes (10 oz). Adults are given 2 to 3 tablespoonfuls daily, children 2 to 3 teaspoonfuls daily. At least 4 to 6 grammes (60—90 grains) are necessary for rectal administration in status epilepticus, for intravenous application about 4 grammes (60 grains).

### Uzara.

Uzara is the name of a drug which has recently been therapeutically employed, according to the communications of C. Bachem, A. Gürber, F. Loening and Bruns, in the treatment of dysenteric intestinal disturbances and dysmenorrhœic troubles. The origin of the drug has not yet been definitely settled. According to A. Hopf, it comes from a small shrub indigenous to the African lake district, presumably belonging to the natural order Asclepiaceæ. The roots of this plant contain the active substances, which have not as yet been more fully investigated. The drug, according to Gürber, contains neither alkaloids nor tannic acids; but it contains 3 substances, of which 2 are probably glucosides, which contain no nitrogen and give beautiful colour reactions with concentrated sulphuric acid. The drug is put on the market for therapeutic use in the form of tablets, liquor and suppositories. Nine tablets a day are, according to Bachem, given for diarrhœa, but as many as 4 may be given every 2 hours. The dose of liquor uzara is 30 drops every 2 hours for adults, and for children from 6 drops upwards, according to age.

### Valyl.

This derivative of valerianic acid\*) was prescribed with benefit by E. Diruf, and by other authors before him, for neurasthenia, insomnia after debilitating diseases and troublesome climacteric disturbances. He was able to confirm its beneficial influence on himself, as he was suffering from nervous debility as a result of recurrent influenza, which forced him to take a rest from his medical practice. The debility lasted so long that he decided to take 2 to 3 perles of valyl 3 times a day. As a result, the troublesome insomnia and the other so-called nervous symptoms, e. g., the residues of the first and second attacks of influenza, completely disappeared within 2 to 3 weeks. He therefore recommends valyl for use in similar indications.

Bachem, Berliner klinische Wochenschrift 1911, p. 1514.

Gürber, Münchener medizinische Wochenschrift 1911, p. 2100.

Loening, Münchener medizinische Wochenschrift 1911, p. 2354.

Bruns, Münchener medizinische Wochenschrift 1911, p. 2250.

\*) Compare Merck's Report 1901.

Diruf, Medizinische Klinik 1911, p. 1204.

**Veratrum.**

In a publication on the treatment of eclampsia gravidarum, E. G. Zinke points out the value of *Veratrum viride*, the employment of which was formerly recommended by Baker and Reamy\*). He prescribed *tinctura veratri viridis* together with hot packs, baths, strict milk diet and not too vigorous purgation. In every case, no matter how many attacks had already occurred, the drug was injected subcutaneously in doses of 20 drops every hour, until the pulse rate was reduced to 60 per minute. If it showed a tendency to increase in frequency again, 10 to 15 drops were injected immediately, and this treatment was continued until the pulse rate had fallen to 60. So long as the pulse rate remained at or slightly below 60, the medication was discontinued. Tincture of veratrum was only in exceptional cases administered internally. The effect of this method of treatment had a remarkably rapid effect in individual cases. In a few cases the injections were continued for days and weeks; one patient was even given 3 to 4 injections of 10 to 15 drops of tincture of veratrum daily for 2 months. By means of this treatment, Zinke was able to reduce the maternal mortality by more than 50 p. c., while there was a slight but constant increase in the mortality of the children.

Zinke states that he used Norwood's tincture of veratrum, which is prepared from *Veratrum viride* (American hellebore) in the proportion of 4 in 10, like the tincture of American hellebore of the U. St. Ph., 1870\*\*). In the present American pharmacopœia the proportion is given as 1 in 10. The dose of 20 drops of the 40 p. c. tincture is apparently somewhat large, but the value of the preparation is most probably due to its large dosage; R. de Cotret even used to inject 20 drops of fluid extract of veratrum, a dose which considerably exceeds that suggested by Zinke.

**Veronal and Veronal-Sodium.**

Veronal is becoming more and more appreciated as an efficacious hypnotic in all branches of therapeutics, for in

Zinke, Deutsche medizinische Wochenschrift 1911, p. 1351.

\*) Compare Merck's Report 1902, p. 64.

\*\*) The Dispensatory of the United States of America, Sixteenth Edition, p. 1537.

Cotret, Presse médicale 1902, p. 1125.

recent years special attention has been paid to correct dosage and indications, and thus any secondary effects of the drug have been avoided. The employment of veronal in psychiatric and in neurological practice has been discussed by A. Diehl, L. Edinger, Marie and Ranson and Scott. Diehl prescribed veronal for his patients in series of several days; even in obstinate insomnia he usually gave only 0.5 gramme ( $7\frac{1}{2}$  grains), and only in exceptional cases did he prescribe 0.75 to 1.0 gramme (12—15 grains) in order to avoid failures at the beginning of a course of veronal treatment, reducing the dose to 0.5 gramme ( $7\frac{1}{2}$  grains) on the third day. He always found this amount to suffice. In his experience veronal never had a harmful effect when given in the ordinary doses, and even on prolonged administration it gave rise to no bad effects. By its use a refreshing night's sleep is followed by a day during which the patient feels full of vigour for work; at the most a slight need for rest is felt at midday, in consequence of which the midday sleep may supervene more rapidly, but only if the patient desires to sleep. The author frequently noticed that veronal sleep closely resembles physiological sleep. He considers veronal specially valuable for procuring a dreamless sleep for restless persons, who are addicted to exciting dreams.

Edinger also states that veronal (or veronal-sodium) acts promptly and certainly, usually even in small doses. He never observed unpleasant secondary effects in his practice. In his experience, veronal takes the place of all other hypnotics, old or new; he is also of opinion that one hypnotic should be adhered to, in order that exact knowledge may be gained of its method of employment. Very small doses suffice if veronal-sodium be combined with antipyrin and bromide, as in the following formula:

Rp. Veronal-sodium	3.5 grammes (53 grains)
Antipyrin	1.0 gramme (15 „ )
Pot. brom.	10.0 grammes ( $\frac{1}{3}$ oz)
Aq. destill.	ad 150.0 „ (5 oz)

One spoonful (15 grammes [ $\frac{1}{2}$  oz]) of this mixture is given to the patient for 2 to 3 days at night time. Then the 15 grammes

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Diehl, Monatsschrift für Psychiatrie und Neurologie 1911, p. 450.

Edinger, Jahreskurse für ärztliche Fortbildung 1911, No. 5.

Marie, Archives de neurologie 1911, June.

Ranson Scott, American Journal of Medical Sciences 1911, p. 673.

( $\frac{1}{2}$  oz) are placed beside his bed at night with instructions that he is to manage with as little as possible, but that he may take the whole dose if a part is inefficacious. In this manner most people can soon get on with quite small doses and after a few weeks dispense with the drug altogether.

Marie obtained very good results with veronal in insomnia due to melancholia with delusions of persecution, in general paralysis, senile dementia, mental confusion, delirium with hallucinations, morphinism, conditions of excitement due to epilepsy, etc. The communications of Ranson and Scott on the value of veronal in delirium tremens are equally satisfactory. But in these cases it should not be given as a routine treatment, and only until the tremor has subsided. The authors' statement, that the mortality in delirium tremens is appreciably lower when veronal is used than when it is not used, is noteworthy.

C. von Noorden found that a combination of 0.3 gramme (5 grains) of veronal with 0.25 gramme (4 grains) of phenacetin possesses the same hypnotic action as 0.6 gramme (10 grains) of veronal. This combination is specially suitable for cases in which large doses of veronal are for any reason undesirable. If a troublesome cough is a partial cause of the insomnia, the author recommends the addition of 0.025 to 0.03 gramme ( $\frac{2}{5}$ — $\frac{1}{2}$  grain) of codeine phosphate to the combination mentioned above. This drug is also useful in other cases of obstinate insomnia, as it serves to strengthen the action of the veronal to an extraordinary degree.

Veronal is undoubtedly the best remedy for the treatment of sea-sickness. This opinion is also expressed in E. Schepelmann's comprehensive work on sea-sickness. The usefulness of veronal or of veronal-sodium also finds confirmation in the communications of H. Citron, O. Muller, and Canivez. Citron draws attention to the fact that the rectal application of the drug is also efficacious. For this purpose suppositories containing 0.5 gramme ( $7\frac{1}{2}$  grains) of

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Noorden, Therapie der Gegenwart 1911, No. 6.

Schepelmann, Klinisch-therapeutische Wochenschrift 1911, No. 40—51.

Citron, Berliner klinische Wochenschrift 1911, No. 36.

Muller, Le Scalpel 1911, No. 18.

Canivez, Le Scalpel 1911, No. 19.

veronal-sodium are used. As a rule, veronal medication is followed in the course of an hour by a sensation of comfort and well-being, and an improvement in the appetite, while the feeling of discomfort disappears. Veronal-sodium may be used with equal benefit for so-called train-sickness as well as for sea-sickness. Muller, like Canivez, obtained good results from its use as a prophylactic. In gastric disturbances with nervous symptoms, veronal, given in very small doses, is most useful. M. Meyer administered it with good results in doses of 0.015 to 0.03 gramme ( $\frac{1}{4}$ — $\frac{1}{2}$  grain), in combination with other suitable drugs, such as sodium bicarbonate, nux vomica, hydrastis canadensis, pepsin wine, rhubarb and other stomachics in acute gastric catarrh, flatulence, dyspepsia, fermentative gastritis with heartburn, anorexia, epigastric pain and emaciation, etc.

The pharmacological investigation of C. Römer, C. Jacoby, C. Bachem and A. Gröber can only be referred to here. It may, however, be noted that Gröber, in experiments on animals, found that veronal had a paralysing action on the gastric vessels and in consequence lowers the blood pressure, and he therefore advises against the use of the drug in the presence of injuries to the vascular functions, such as occur in typhoid fever. In cases of poisoning he advises warmth and gastric lavage. Besides this, oxygen should be administered and a weight applied to the abdomen with the object of compressing the vessels. E. Klausner describes a case of veronal poisoning, in which after 2 doses of 0.5 gramme ( $7\frac{1}{2}$  grains) of veronal, besides transient cutaneous affections, disturbances of the sensorium, etc., albuminuria occurred which, with rest in bed and milk diet, disappeared in the course of a week.

### Yeast.

The following notes give a brief synopsis of the literature published last year on the yeast preparations.

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Meyer, Merck's Archives 1911, No. 1.

Römer, Jacoby, Archiv für experimentelle Pathologie 1911, Vol. 66, p. 241—312.

Bachem, Klinisch-therapeutische Wochenschrift 1911, p. 509.

Gröber, Biochemische Zeitschrift 1911, Vol. 31, p. 1.

**Bajuvarin.** Ch. Steffen used this preparation with good results in veterinary practice, in foot-and-mouth disease. As he attributes the action of the yeast to the process of fermentation, he prescribed it in combination with sugar of milk; two tablespoonfuls of the mixture were given to the cows morning and evening; the mixture was mixed with warm milk and introduced into the animal's mouth. Externally the author applied bajuvarin in the form of an ointment to the clefts of the hoof, which had previously been cleansed. This ointment is also said to be useful in disease of the teats connected with the above named disease. Steffen has also used the preparation for other skin diseases of domestic animals. His indications are the same as those for yeast generally.

**Fermentin.** This, according to Schmatolla, is a stable preparation containing benzoin. Like all preparations of yeast, it may be used both internally and externally for a variety of skin diseases, such as acne, furunculosis, pityriasis, alopecia eczematosa, lichen, psoriasis, leucorrhœa, etc. Dreuw recommends it in the form of soaps, which may be combined with other remedies, such as salicylic acid and sulphur.

**Fermocyl**, a yeast preparation issued in tablet form\*), was tried by H. Seemann in diabetes; for yeast has long been used, and in some cases with good results, in the treatment of glycosuria. The author prescribed 3 fermocyl tablets 3 times a day, besides opium and a suitable diet, and he states that the sugar in the urine decreased, in spite of no change having been made in the amount of carbohydrates ingested. L. von Korczynski and Scherk also recommend fermocyl tablets in diabetes, as well as in intestinal affections and for diseases of the skin.

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Steffen, *Berliner tierärztliche Wochenschrift* 1911, p. 25 and 746.  
Dreuw, *Monatshefte für praktische Dermatologie* 1911, Vol. 52, p. 349.

\*) A mixture of dried yeast, powdered pancreas and sodium phosphate. 1 tablet corresponds to about 2 grammes (30 grains) of fresh yeast.

Seemann, *Fortschritte der Medizin* 1911, No. 24.

Korczynski, *Österreichische Ärzte-Zeitung* 1911, No. 10.

Scherk, *Klinisch-therapeutische Wochenschrift* 1911, No. 20.

**Myco der min.** This stable yeast preparation was prescribed internally by P. Atanackovic for typhoid fever with multiple skin abscesses, and for furunculosis. Externally it has been used for gonorrhœal arthritis, and for suppuration of the middle-ear, mixed with kaolin or sugar. In a large number of cases the action was satisfactory.

**Xerase.** A. P. Samoilow, R. Tojbin and E. Cronbach have reported upon the use of the preparation of yeast and kaolin known under the name of xerase. According to Samoilow, the action of this preparation, which consists of yeast, kaolin, glucose and physiological nutrient salts, is due to the fact that the application of xerase to inflamed mucous membranes or to tissues deprived of their epidermis causes the rapid absorption of purulent secretions. The author has obtained very good results in his gynæcological practice both in gonorrhœal and in non-gonorrhœal diseases.

Cronbach's investigations as to the value of the yeast preparations, which form a continuation of the work of Abraham, in contradistinction to the findings of other observers, led to the conclusion that yeast has no influence on the gonococcus, but that the fermentation of the yeast probably leads to the formation of bactericidal substances. Therefore the bactericidal power of every yeast preparation with regard to its effect on gonococci should be tested. He considers the favourable action of xerase to be due to a mechanical effect. The fermentation of the yeast causes the kaolin, the mechanical and detergent action of which may be taken for granted, to be thrown against the vaginal wall, where it can exert its favourable action on the course of the disease. As the fermentative action of xerase only lasts for 3 to 4 hours, it is advisable to remove the residue, which might prove a suitable nutrient medium for the gonococci, by cleansing the mucous membrane by means of solution of hydrogen peroxide. The introduction and removal of the xerase should be repeated 2 to 3

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Atanackovic, Österreichische Ärzte-Zeitung 1911, No. 24.

Samoilow, Fortschritte der Medizin 1910, No. 47.

Tojbin, Medizinische Klinik 1911, p. 378.

Cronbach, Allgemeine medizinische Zentralzeitung 1911, p. 63.

Abraham, Merck's Report 1910, p. 180.

times After the removal of the residue of xerase, treatment by means of silver salts may be carried out. Bauer's conclusions are similar to those of Cronbach; he also removed the xerase after 24 hours, as it gave rise to an offensive odour when left for 48 hours. His results in endometritis, erosions, colpitis, vulvo-vaginitis and proctitis, and also in leucorrhœa, were most satisfactory. In gonorrhœa in the male, however, Manasse found gonococci in the secretion 5 to 6 hours after the introduction of bougies of zymin or xerase. Tojbin had similar results in the treatment of vulvo-vaginitis accompanied by leucorrhœa in two children; the vulvo-vaginitis did not improve and gonococci were still present at the end of the treatment. In one case, however, the proctitis was completely cured. On the whole, the author was very favourably impressed by the value of xerase. Erosions, according to him, are always cured. The discharge was diminished in every case and altered in character, becoming paler and more liquid. The inflammatory symptoms on the visible mucous membranes cleared up, but the gonococci only disappeared in the adult patients.

### Yohimbine.

G. Fritsch reports upon a new use for yohimbine. The author starts from the assumption that a drug, which like yohimbine has a stimulating effect on the sexual centres, the nerves radiating from them or the muscular endings, must have a corresponding effect on the uropoietic system. In disturbances of the uropoietic system, which occur for the most part in advanced age (but also in middle age), Fritsch considers that the inevitable senile atrophy of the organs should be treated by suitable measures. For this purpose he recommends yohimbine, moderate doses of which exert a tonic action on the musculature of the bladder. It is sufficient to give one yohimbine tablet (0.005 gramme [ $\frac{1}{12}$  grain]) for 3 to 4 days and then to allow an interval of 3 days. As a result of this medication the strangury and incontinence of urine were cured. Larger experimental doses (3 tablets a

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Bauer, Manasse, Allgemeine medizinische Zentralzeitung 1911, p. 63.

Fritsch, Deutsche medizinische Wochenschrift 1911, p. 1266.

day) led to slight general excitability and more vigorous cardiac action, without troublesome secondary symptoms.

### **Zinc-Perhydrol.**

In the treatment of ulcers of the leg, zinc-perhydrol has, according to E. H a n s c h m i d t, proved of extraordinary value. The author describes a case of extensive varicose ulcer, which had been unsuccessfully treated for 6 years with a variety of measures, such as lunar caustic, compresses, powders and ointments. When zinc-perhydrol treatment was begun, the wound was in a gangrenous condition, extending almost to the periosteum, surrounded by œdema and having infiltrated, undermined edges. In this case zinc-perhydrol, applied in the form of a 25 p.c. ointment, effected a rapid cleansing of the wound by throwing off the gangrenous tissue, and in a fortnight the wound consisted of a red, granulated surface with firm, healing edges. A firm cicatrix resembling skin resulted and it is specially noteworthy that there was no recurrence. The author particularly points out that this treatment does not interfere with the patient's occupation.

Zinc-perhydrol proved very useful in burns, particularly in recent burns of the first and second degree. The application of the 25 p.c. ointment immediately alleviates the pain and facilitates the change of dressings. But Hanschmidt has also obtained good results in burns of the third degree, accompanied by deep lacerated wounds and complicated bone injuries, such as result from explosions.

The treatment of cellutic processes affords a further field of usefulness for zinc-perhydrol. In whitlows, abscesses, furuncles and carbuncles, after incision and removal of the necrotic core, the author filled up the wound cavity with a 25 p.c. ointment, and healing rapidly resulted. For infected wounds, a 25 p.c. ointment should be used, and a 10 p.c. ointment for small, clean cuts and lacerations. The ointment is spread on gauze and applied to the wound. Very septic wounds should be washed out with a 3 p.c. perhydrol solution before applying the ointment. Zinc-perhydrol is particularly valuable in country practice, as the dressing only requires changing

every 3 to 5 days, and no other antiseptic is required, as the wound surface is always clean. The author also points out that zinc-perhydrol has a definite anæsthetic and hæmostatic action, which in cases of burns and deep lacerated wounds is a valuable adjunct to the other useful properties of the preparation.

With regard to a combination of zinc-perhydrol with amido-azotoluol, compare page 146 of this Report.

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